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(54) Title: NOVEL BIOMARKERS OF TYROSINE KINASE INHIBITOR EXPOSURE AND ACTIVITY IN MAMMALS

| Percent Change in Plasma Proteins 12 hr post 2 <sup>nd</sup> dose /pre-dose |                                  |                |        |  |          |                           |              |       |      |       |        |     |  |
|---|----------------------------------|----------------|--------|--|----------|---------------------------|--------------|-------|------|-------|--------|-----|--|
|   |                                  |                |        | SU6668.004 BID (Tablets) Plasma/Pharmacokinetics for Day 1 |          |                           |              |       |      |       |        |     |  |
| Pt #  | SU6668 Dose (mg/m <sup>2</sup> ) | cancer type    | gender | SU6668 Cmax (ug/mL)  | Tmax hrs | Exposure >2.3 ug/mL (hrs) | AUC ug*hr/mL | PAI-1 | VEGF | MMP-9 | TIMP-1 | TF  |  |
| 28  | 400                              | prostate       | M      | 13.0   | 15.0     | 21.3                      | 164.3        | 297   |      | 46    | 27     | 21  |  |
| 32  | 300                              | ovarian        | F      | 12.9   | 2.0      | 11.8                      | 85.7         | 19    | 94   | -45   | -3     | 18  |  |
| 34  | 300                              | laryngeal      | M      | 11.6   | 3.5      | 10.7                      | 136.4        | 63    | -1   | 156   | -2     | 5   |  |
| 17  | 200                              | colon          | F      | 11.5   | 2.0      | 11.0                      | 66.1         | 221   |      |       | 105    | 24  |  |
| 25  | 300                              | colon          | M      | 11.0   | 2.0      | 13.4                      | 75.5         | 7     | -27  | 184   | 69     | 22  |  |
| 27  | 400                              | colon          | M      | 10.3   | 6.0      | 9.1                       | 71.2         | -40   | 10   | -15   | -5     | 32  |  |
| 19  | 200                              | leiomyosarcoma | F      | 9.5  | 4.0      | 12.8                      | 80.2         | 104   | 95   | 36    | 0.2    | 12  |  |
| 23  | 300                              | renal          | F      | 9.3  | 2.0      | 8.0                       | 53.5         | -69   | -36  | -79   | -9     | 9   |  |
| 16  | 200                              | thyroid        | F      | 9.3  | 2.0      | 7.3                       | 55.7         | 263   |      | 409   | 43     | 37  |  |
| 24  | 300                              | leiomyosarcoma | F      | 8.2  | 4.0      | 16.4                      | 71.2         | 62    | 9    | 18    | 27     | 39  |  |
| 30  | 300                              | testicular     | M      | 7.9  | 1.0      | 2.1                       | 32.9         | 52    | 82   | -66   | 13     | -1  |  |
| 33  | 300                              | testicular     | M      | 7.5  | 5.0      | 10.4                      | 43.2         | -20   | 121  | 305   | 99     | 212 |  |
| 31  | 300                              | hepatocellular | F      | 6.9  | 4.0      | 7.3                       | 55.8         | 29    | 100  | 1     | 0      | 227 |  |
| 20  | 200                              | prostate       | M      | 5.9  | 2.5      | 10.9                      | 68.5         | -47   | 181  | 48    | 40     | 38  |  |
| 26  | 300                              | prostate       | M      | 5.6  | 2.0      | 8.2                       | 57.0         | 2     | 50   | 38    | 21     | 8   |  |
| 15  | 200                              | breast         | F      | 5.3  | 2.0      | 4.8                       | 44.0         | 95    | 10   | -1    | 14     | 9   |  |
| 35  | 300                              | thyroid        | M      | 4.3  | 1.5      | 16.1                      | 97.5         | -65   | 24   | -19   | 64     | 65  |  |
| 22  | 300                              | colon          | M      | 2.5  | 4.0      | 0.5                       | 20.8         | -14   | 23   | 29    | -3     | -5  |  |
|   | >500%                            |                |        |  |          |                           |              |       |      |       |        |     |  |
|   | 29 to 500 %                      |                |        |  |          |                           |              |       |      |       |        |     |  |
|   | -66 to 28%                       |                |        |  |          |                           |              |       |      |       |        |     |  |

(57) Abstract: The present invention describes novel methods that measure in a mammal the level of at least one biomarker, such as a protein and/or mRNA transcript. Based on the level of at least one biomarker in a mammal exposed to a test compound, compared to the level of the biomarker(s) in a mammal that has not been exposed to a test compound, the ability of the test compound to inhibit tyrosine kinase activity can be determined. The invention also relates to novel methods, wherein a change in the level of at least one biomarker in a mammal exposed to a compound, compared to the level of the biomarker(s) in a mammal that has not been exposed to the compound, indicates whether the mammal is being exposed to, or is experiencing or will experience a therapeutic or toxic effect in response to, a compound that inhibit tyrosine kinase activity.



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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

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[0001] This application claims benefit of priority from U.S. provisional application Ser. Nos 60/380,872, filed May 17, 2002, 60/448,922, filed February 24, 2003, and 60/448,874, filed February 24, 2003, all of which are incorporated by reference in their entirety.

### **BACKGROUND OF THE INVENTION**

[0002] A biomarker is a molecular marker of a biological event or phenomenon in a organism. Changes in the level of certain biomakers indicate a biological response to a chemical compound in an organism. Biological responses include events at the molecular, cellular or whole organism level. Changes in biomarker levels can be measured and used to indicate whether or not a particular effect has been achieved in the organism. Changes in biomarker levels can indicate that an organism has been exposed to a particular compound. Changes in biomarker levels also can indicate whether an organism is experiencing or will experience a therapeutic effect or even a toxic event in response to a compound.

### **SUMMARY OF INVENTION**

[0003] The present invention relates to novel methods comprising measuring in a mammal the level of at least one biomarker, such as a protein and/or mRNA transcript. In the novel methods, the level of at least one biomarker in a mammal exposed to a compound is compared to the level of the biomarker(s) in a mammal that has not been exposed to the compound.

[0004] The invention includes methods for determining whether a test compound inhibits the activity of a protein tyrosine kinase. The invention further relates to methods for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity. The invention also discloses methods for determining if a mammal is responsive to the administration of a compound that inhibits tyrosine kinase activity. In addition, the invention relates to methods for identifying mammals that will respond therapeutically to a compound that inhibits VEGFR and/or PDGFR tyrosine kinases. The invention further discloses methods for testing or predicting, as well as kits for determining, whether a mammal will respond therapeutically to a compound that inhibits tyrosine kinase activity. The invention also relates to methods for testing or predicting whether a mammal

will experience an adverse event, such as fatigue, in response to a method of treatment comprising administering a compound that inhibits tyrosine kinase activity.

[0005]

### **BRIEF DESCRIPTION OF THE FIGURES**

[0006] Figure 1 shows the levels of various plasma proteins in plasma from human patients, measured by ELISA, before and 24 hours after the first dose of Compound A (SU6668).

[0007] Figure 2 shows the abundance of a protein (spot #5) in patient plasma, measured by 2D polyacrylamide gel analysis, before and 4 hours after the first dose of Compound A (SU6668).

[0008] Figure 3 shows the identification by mass spectrometry analysis of spot #5 from the 2D gel analysis of patient plasma analyzed in Figure 2.

[0009] Figure 4A shows the change in level of various RNA transcripts, before versus 24 hours after the first dose of Compound A (SU6668), in patient whole blood, as measured by Taqman and DNA Array analysis. Figure 4B shows the change in the level of vinculin RNA, before versus 24 hours after the first dose of Compound A (SU6668), in patient whole blood, as measured by Taqman and DNA Array analysis.

[0010] Figure 5 shows the levels of various RNA transcripts, in patient blood samples, on treatment day 28 (27 days after the first dose of Compound A) versus the levels on treatment day 0 (before treatment with Compound A). Numbers shown indicate increase and/or decrease relative to baseline on day 0. No significant change is shown as ~1. Levels decreased are less than 1 and levels increased are greater than 1.

[0011] Figure 6 shows the differential expression of candidate biomarker transcripts in patient PBMC at day 56 relative to day 1 of therapy. The diagram is a depiction of the Affymetrix Difference Calls assigned to each day 56:day 1 expression comparison among the patient sample pairs analyzed via GeneChip hybridization analysis. Letters within blocks represent the Difference Call assigned to each relative expression comparison. The abbreviations are: I = Increase, MI = Marginally Increased, NC = Not Changed; MD = Marginally Decreased; D = Decreased. Cases in which an Increased or Marginally Increased call is assigned to a day 56:day 1 comparison are shaded in gray. Each column represents a different patient. Column headings in each grid represent patient response assessed at the end



of first treatment cycle: PR = partial response, CR = complete response, PD = progressive disease.

**[0012]** Figures 7A and 7B show the percentage of patients with increased expression of biomarker transcripts following treatment with Compound B (SU5416). Differential expression of six transcripts as measured by microarray and quantitative RT-PCR is presented. The percentage of cases in 5-FU/LV (control) and 5-FU/LV + SU5416 trial arms with increased expression (at predose day 56 relative to predose day 1) of each transcript is displayed. Figure 7A shows the results of the Affymetrix analysis and Figure 7B shows the results from SYBR Green RT-PCR. For the SYBR Green data, an increased is defined as relative expression value of 2-fold or greater. A total of 31 sample pairs were used in RT-PCR analysis; 18 were from SU5416 arm (5 PR, 1 CR, 11 PD and 1 SD response at end of cycle 1), and 13 were from the control arm (9 PR, 3 PD and 1 SD).

**[0013]** Figure 8 shows the percentage of patients with increased expression of four biomarker transcripts, following treatment with Compound B (SU5416). Differential expression of four transcripts as measured by quantitative RT-PCT is presented. Percentage of cases in CPT-11/5-FU/LV (control) and CPT-11/5-FU/LV + SU5416 trial arms with increased expression (at predose day 42 relative to predose day 1) of four candidate biomarker transcripts in a second SU5416 Phase III clinical trial is displayed. The convention is the same as in panel B in Figure 7. A total of 36 sample pairs was included in this analysis; 18 from the Compound B arm and 18 from the control arm (8 PR and 10 SD responses at end of cycle 1 in each group).

**[0014]** Figure 9 shows hierarchical clustering of relative expression ratios for four biomarker transcripts. This mosaic depicts association between patient samples and relative expression of the four potential biomarker transcripts. Natural log-transformed SYBR Green RT-PCR ratio data (relative expression of day 56:day 1) were used in analysis. In the color scheme, higher ratios are indicated in red, lower ones in green (scale ranges from -4 to +4). Results from individual patients are oriented as rows and transcripts are oriented as columns. Red bars on the right side of the map indicate cases from the SU4316 arm. The hierarchical clustering method is average linkage and the distance metric is Euclidean.

**[0015]** Figure 10 shows PAI-1 levels on day 1 and day 56 in patient plasma samples. MR = minor response (cycle 1); PR = partial response (cycle 1); PD = progressive disease (cycle 1)

**[0016]** Figure 11 shows the mRNA and protein sequences for lactoferrin (SEQ ID NOS 68-69, respectively), lipocalin-2 (SEQ ID NOS 70-71 and 180, respectively), MMP9 (SEQ ID NOS 72 & 66, respectively), and CD24 (SEQ ID NO: 73-74, respectively).

**[0017]** Figure 12 shows mRNA and protein sequences for eucaryotic initiation factor 4A11 (SEQ ID NOS 75-76, respectively), human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06792) (SEQ ID NOS 77-78, respectively), Homo sapiens thymosin beta-10 (SEQ ID NOS 79-80, respectively), Homo sapiens hnRNPcore protein A1 (SEQ ID NOS 81-82, respectively), human leucocyte antigen (CD37) (SEQ ID NOS 83-84, respectively), human MHC class II HLA-DR beta-1 (SEQ ID NOS 85-86, respectively), Homo sapiens translation initiation factor eIF3 p66 subunit (SEQ ID NOS 87-88, respectively), Homo sapiens nm23-H2 gene (SEQ ID NOS 89-90, respectively), human acidic ribosomal phosphoprotein P0 (SEQ ID NOS 91-92, respectively), human cyclophilin (SEQ ID NOS 93-94, respectively), Genbank Accession No. AI541256 (cDNA) (SEQ ID NO: 95), human T-cell receptor active beta chain (SEQ ID NOS 96-97, respectively), human MHC class II lymphocyte antigen (HLA-DP) beta chain (SEQ ID NOS 98-99, respectively), human KIAA0195 (SEQ ID NOS 100-101, respectively), Homo sapiens MAP kinase kinase 3 (MKK3) (SEQ ID NOS 102-103, respectively), human beta-tubulin class III isotype (beta-3) (SEQ ID NOS 104-105, respectively), human tropomyosin (SEQ ID NOS 106-107, respectively), 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C (SEQ ID NOS 108-109, respectively), human MLC emb gene for embryonic myosin alkaline light chain (SEQ ID NOS 110-111, respectively), Homo sapiens glyoxalase II (SEQ ID NOS 112-113, respectively), Homo sapiens trans-golgi network glycoprotein 48 (SEQ ID NOS 114-115, respectively), histone H2B (SEQ ID NOS 116-117, respectively), human RLIP76 protein (SEQ ID NOS 118-119, respectively), Genbank Accession No. W26677 (human retina cDNA) (SEQ ID NO: 120), human PMI gene for a putative receptor protein (SEQ ID NOS 121-122, respectively), human DNA-binding protein A (dbpA) (SEQ ID NOS 123-124, respectively), human ITIH4 (SEQ ID NOS 125-126, respectively), IL-8 (SEQ ID NOS 182-183, respectively) and C-reactive protein (SEQ ID NOS 184-185, respectively).

**[0018]** Figure 13 shows the changes in VEGF plasma levels, as measured by ELISA, in patients receiving a malate salt of Compound 1 in Trial C.

**[0019]** Figure 14 shows by hybrid ELISA that VEGF/PLGF heterodimers are detected in plasma of cancer patients and are induced in patients after treatment with a malate salt of Compound 1 in Trial C. The hybrid ELISA assay demonstrates that levels of

heterodimers are increased in 3 of 3 patients tested, and follow a pattern of induction similar to that seen for VEGF and PLGF.

[0020] Figure 15 shows that plasma levels of soluble VEGFR2 decrease in patients in Trial D following treatment with a malate salt of Compound 1 in a dose-dependent manner.

[0021] Figure 16 shows that the decrease in sVEGFR2 following treatment with Compound 1 or malate salt thereof correlates with AUC values (end of C1 dosing, all trials). The scatter graph plots sVEGFR2 fold change (end of cycle 1 dosing over baseline) against AUC values from end of cycle 1 dosing. Results from the first 44 patients (representing 4 trials) are included.

[0022] Figure 17 shows that chemokine MIG is induced in patients during treatment with a malate salt of Compound 1. MIG is a biomarker that also correlates with tumor responses as measured by <sup>18</sup>FDG-PET imaging. Results are from Trial C.

[0023] Figure 18 discloses the amino acid sequence of human vascular endothelial growth factor (VEGF) (SEQ ID NO: 127).

[0024] Figure 19 discloses the amino acid sequence of human placenta growth factor (PLGF) (SEQ ID NO: 128).

[0025] Figure 20 discloses the amino acid sequence of human vascular endothelial growth factor receptor 2 (VEGFR2) (SEQ ID NO: 129).

[0026] Figure 21 discloses the amino acid sequence of human Monokine Induced by Interferon-Gamma (MIG) (SEQ ID NO: 55).

[0027] Figure 22 discloses the amino acid sequence of human interferon-inducible cytokine IP-10 (SEQ ID NO: 130).

[0028] Figure 23 discloses the amino acid sequence of human Interferon-inducible T-cell alpha chemoattractant (I-TAC) (SEQ ID NO: 131).

[0029] Figure 24 shows cDNA or mRNA sequences for human vinculin (SEQ ID NOS 132 & 181, respectively), basic transcription factor 3 homologue (SEQ ID NO: 133), human c-jun proto oncogene (SEQ ID NO: 134), human c-fos proto-oncogen (SEQ ID NO: 135), Homo sapien PTP-nonreceptor type 2 (SEQ ID NO: 136), human cdc2-related protein kinase (SEQ ID NO: 137), human cyclin C (SEQ ID NO: 138), human DNA polymerase-gamma (SEQ ID NO: 139), protein kinase C-alpha (SEQ ID NO: 140), lipocortin II/annexin

A2 (SEQ ID NO: 141), histone H2B member R (SEQ ID NO: 142), Homo sapien amphiregulin (SEQ ID NO: 143), human basic transcription factor 3 (SEQ ID NO: 144), Homo sapien phosphoinositide-3-kinase p110 subunit (SEQ ID NO: 145), human gelsolin (SEQ ID NO: 146), Homo sapien Cyclin D2 (SEQ ID NO: 147), ephrin receptor (EphB4) (SEQ ID NO: 148), human Hanukah factor/granzyme A (SEQ ID NO: 149), von Hippel-Lindau (VHL) tumor suppressor (SEQ ID NO: 150), human mRNA for OB-cadherin-1 (SEQ ID NO: 151), human mRNA for OB-cadherin-2 (SEQ ID NO: 152), phosphoinositol 3-phosphate-binding protein-3 (PEPP3) (SEQ ID NO: 153), human phosphoinositol 3-kinase p85 subunit (SEQ ID NO: 154), human mucin 1 (SEQ ID NO: 155), ErbB3/HER3 receptor tyrosine kinase (SEQ ID NO: 156), and Homo sapien gene for hepatitis C-associated microtubular aggregate protein p44 (nine exons) (SEQ ID NOS 157-164, respectively).

[0030] Figure 25 shows that FLT3 ligand (FL) is induced in patients during treatment with Compound 1.

[0031] Figure 26 demonstrates that interleukin-6 (IL-6) is induced in patients during treatment with Compound 1, and that a greater than 2-fold increase in IL-6 plasma concentration after treatment with Compound 1 correlates with patient fatigue.

[0032] Figure 27 demonstrates that C-reactive protein (CRP) is induced in patients during treatment with Compound 1, and that a greater than 2-fold increase in CRP plasma concentration after treatment with Compound 1 correlates with patient fatigue.

[0033] Figure 28 shows that a higher baseline value of CRP in patients with GIST correlates with progressive disease, in Trial D.

[0034] Figure 29 shows that protein expression of OB-cadherin 1 (cadherin 11) is up-regulated in Colo205 xenograph tumors after exposure to Compound 1 for 24 or 48 hours.

#### **BRIEF DESCRIPTION OF THE TABLES**

[0035] Tables 1-22 appear following the Examples disclosed in this application, and specifically after Section K.

[0036] Table 1 shows Compound B (SU5416) PBMC sample processing history for Trial A.

[0037] Table 2 shows a list of biomarker transcripts as detected in Affymetrix analysis.

[0038] Table 3 shows primer sequences used in RT-PCR validation analysis.

[0039] Table 4 shows a Mann-Whitney U Test comparison of expression fold change data from Compound B and control arms (Trial A). This statistical analysis was performed to assess the significance of differences in expression change ratios (day 56 vs day 1) between the Compound B and control arms. Separate comparisons were performed of expression change values from Affymetrix analysis and from SYBR Green RT-PCR validation experiments. P-values  $\leq 0.05$  were considered statistically significant.

[0040] Table 5 shows the Mann-Whitney U Test of Compound B expression data in Trial B.

[0041] Table 6 shows a summary of class prediction results for pooled data (3 gene predictor set).

[0042] Table 7 shows changes in plasma levels of PLGF in patients in Trial C receiving daily treatment with a malate salt of Compound 1.

[0043] Table 8 shows changes in plasma levels of MIG, IP-10, and I-TAC in patients receiving treatment with Compound 1 or a malate salt thereof. Levels of IP-10 and I-TAC at end cycle 1 dosing are estimated values in some cases ( $>500$ ), as the amount of IP-10 or I-TAC in these samples was higher than the highest standard provided for standard curve generation. All patients represented in this table are from Trial C, except for patient 11 from Trial B and patient 9 from Trial A. Patients in Trial C received treatment with a malate salt of Compound 1, while patients from Trials A and B received treatment with Compound 1.

[0044] Table 9 shows changes in PLGF and/or sVEGFR2 plasma levels in cancer patients after receiving treatment with Compound 1 or a malate salt thereof. For PLGF, *italics text* indicates a fold-change of 3-fold or greater, end of cycle 1 dosing relative to day 1. For sVEGFR2, *italics text* indicates a decrease of 30% or more, end of cycle 1 dosing relative to day 1. Patients in Trials C and D received treatment with a malate salt of Compound 1, while patients from Trials A and B received treatment with Compound 1.

[0045] Table 10 shows an increase in MIG plasma levels in cancer patients after receiving treatment with Compound 1 or malate salt thereof. As with Table 2, results are from Trial C except for patient 11 from Trial B and patient 9 from Trial A..

[0046] Table 11A shows the change in levels of various mRNA transcripts isolated from Colo205 xenograft tumors, as measured by DNA Array analysis, before exposure to Compound 1, and 6 hours and 24 hours after exposure to the first dose of Compound 1.

[0047] Table 11B shows the change in levels of various mRNA transcripts isolated from SF767 xenograft tumors, measured by DNA Array analysis, before exposure to Compound 1, and 4 hours and 24 hours after exposure to the first dose of Compound 1.

[0048] Table 12 shows the change in the levels of protein expression and/or mRNA transcript abundance in Colo205 xenograft tumors, as measured by Taqman Real Time PCR, before exposure to Compound 1, and at 6 hours versus 24 hours after exposure to the first dose of Compound 1. The following transcripts were measured: Amphiregulin, Cdc2-related protein kinase, phosphoinositol 3-kinase, p110 subunit, cyclin C, OB-Cadherin1, OB-Cadherin2, p85 subunit, Mucin 1, von Hippel-Lindau (VHL) tumor suppressor, ephrin receptor (EphB4), and Gelsolin.

[0049] Table 13 shows the forward and reverse primer and probe sequences used in the TaqMan Real Time PCR Analysis of Colo205 xenograft tumor samples.

[0050] Table 14 lists three sets of 2D gels used in MALDI-TOF-MS and MALDI-MS/MS analysis.

[0051] Table 15 shows the quantification of Spot #1202 from 2D gel analysis. 2D gel analysis was performed on samples isolated from HUVECs that were stimulated with VEGF after pre-treatment with Compound 1 or vehicle control (DMSO).

[0052] Table 16 shows definitive identification of Spot #1202 as interstitial collagenase precursor (pro-MMP-1), as seen in MALDI-TOF-MS analysis.

[0053] Table 17 identifies Spot #1202 as interstitial collagenase precursor (pro-MMP-1), as seen in MALDI-MS/MS analysis.

[0054] Table 18 shows quantitative ELISA analysis of pro-MMP1 levels in HUVEC conditioned media, after stimulation of HUVEC cells with VEGF after pre-treatment with Compound 1 at 10 nM, 100 nM or 1  $\mu$ M concentrations, or vehicle control (DMSO).

[0055] Table 19 shows an increase pro-MMP1 levels in patient plasma after treatment with Compound 1. Results are from Study B.

[0056] Table 20 lists the analytes measured using Array 1.1 and Array 2.1 in an antibody chip microassay analysis.

[0057] Table 21 lists 23 biomarkers that show changes in plasma levels following treatment with Compound 1. An up arrow, down arrow or (-) denote relative increase, decrease or no change in detected level respectively, in samples for patients 1, 2 and 3. The

accession numbers for markers, not previously described herein, are as follows: ENA-78 (epithelial derived neutrophil activating protein 78) (SEQ ID NO: 48), P42830; MPIF-1 (myeloid progenitor inhibitory factor 1) (SEQ ID NO: 49), P55773; GCP-2 (gamma tubulin complex component 2) (SEQ ID NO: 50), Q9BSJ2; Amphiregulin (Amphireg) (SEQ ID NO: 51), AAA51781; IL-1 $\alpha$  (interleukin-1 alpha) (SEQ ID NO: 52), NP 000566 for preprotein; IL-1 $\beta$  (interleukin-1 beta) (SEQ ID NO: 53), NP000567 for preprotein; IL-2 (interleukin-2) (SEQ ID NO: 54), NP000577 for preprotein; MIG (mitogen inducible gene) (SEQ ID NO: 55), NP 061821; NT4 (neurotrophin 4/neurotrophic factor 5) (SEQ ID NO: 56), NP 006170; IGFBP-1 (insulin-like growth factor binding factor-1) (SEQ ID NO: 57), NP 000587; GRO- $\beta$  (SEQ ID NO: 58), AAA63183; TNFR1 (tumor necrosis factor receptor 1) (SEQ ID NO: 59), P19438; FLT3 ligand (fms-like tyrosine kinase ligand/Flk 2 ligand) (SEQ ID NO: 60), I38440; IL-6 (interleukin-6) (SEQ ID NO: 61), NP-000591; MCP-1 (monocyte chemoattractant protein 1) (SEQ ID NO: 62), P13500; TNF $\alpha$  (tumor necrosis factor alpha) (SEQ ID NO: 63), NP 000585; TARC (thymus and activation regulated chemokine) (SEQ ID NO: 64), Q92583; MMP7 (SEQ ID NO: 65), NP 002414 for preprotein; MMP9 (SEQ ID NO: 66), NP 004985 for preprotein; and leptin (SEQ ID NO: 67), NP000221 for preprotein. Note that accession numbers and SEQ ID NOs in this specification are used to identify cDNAs, mRNAs or proteins of interest, rather limit the biomarkers to specific sequences.

[0058] Table 22 shows the relative fold change of six plasma biomarkers in three patients (denoted 1, 2 and 3) following Compound 1 treatment relative to predose, as measured by two methods: ELISA; and antibody chip technology (MSI).

### **DETAILED DESCRIPTION OF THE INVENTION**

[0059] The present invention relates to novel methods for determining whether a test compound inhibits tyrosine kinase activity and novel methods for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity. The invention also relates to novel methods for determining whether a mammal is experiencing or will experience a particular biological phenomenon, such as a therapeutic effect, “responding” (as defined herein), or an adverse event, in response to a compound that inhibit tyrosine kinase activity.

[0060] The novel methods comprise measuring in a mammal the level of at least one biomarker, such as a protein and/or mRNA transcript. Based on the level of at least one

biomarker in the mammal exposed with a test compound, as compared to the level of the biomarker(s) in a mammal that has not been exposed to a test compound, the ability of the test compound to inhibit tyrosine kinase activity can be determined. The tyrosine kinases of the novel methods include, but are not limited to, those selected from the group of Flk-1 (KDR), c-kit, FLT1, FLT3, PDGFR-alpha, PDGFR-beta, FGFR-1, FGFR-2 and c-fms/CSF-1 receptor.

**[0061]** In certain embodiments, the test compound is an inhibitor of VEGF-mediated signal transduction. In further embodiments, the test compound is an inhibitor of VEGF-mediated tyrosine phosphorylation of a protein kinase, such as Flk-1. In other embodiments, the test compound is an indolinone, as described herein, and also in U.S. Serial No. 10/281,266. In other embodiments, the tyrosine kinase inhibitor comprises compounds described in U.S. Ser. No. 09/783,264, WO 01/60814, U.S. Ser. No. 10/076,140, U.S. Ser. No. 10/281,266, U.S. Ser. No. 10/281,985, U.S. Ser. No. 10/237,966 (now a U.S. provisional application), as well as a U.S. provisional application Ser. No. 60/448,861, filed February 24, 2003 (entitled "Treatment of excessive osteolysis with indolinone compounds"), all of which are hereby incorporated by reference.

**[0062]** Identification of biomarkers that provide rapid and accessible readouts of efficacy, drug exposure, or clinical response is increasingly important in the clinical development of drug candidates. Embodiments of the invention include measuring changes in the expression levels of secreted proteins, or plasma markers, which represent one category of biomarker. In one embodiment, plasma samples, which represent a readily accessible source of material, serve as a surrogate tissue for biomarker analysis.

#### **A. Definitions**

**[0063]** Unless otherwise stated the following terms used in the specification and claims have the meanings discussed below.

**[0064]** "Test compound" refers to any pharmaceutical composition that inhibits or modulates a protein tyrosine kinase.

**[0065]** "Tyrosine kinase modulator" or "tyrosine kinase inhibitor" refers to any chemical composition that modulates, affects, alters, inhibits or reduces the enzymatic activity or tyrosine phosphorylation action of a tyrosine kinase.



**B. Biomarkers Modulated in Mammals Exposed to Tyrosine Kinase Inhibitors**

**[0066]** In one embodiment, the invention includes a method for determining whether a test compound inhibits tyrosine kinase activity in a mammal, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcript measured in (c), compared to the level of protein and/or mRNA transcript measured in step (a) indicates that the test compound is an inhibitor of tyrosine kinase in the mammal.

**[0067]** Alternatively, a method for determining whether a test compound inhibits tyrosine kinase activity in a mammal comprises:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the compound is an inhibitor of tyrosine kinase in the mammal.

**[0068]** In an other embodiment, the invention includes a method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated

microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA measured in (c), compared to the level of protein and/or mRNA in step (a) indicates that the mammal has been exposed to a test compound that inhibits tyrosine kinase activity.

**[0069]** Alternatively, a method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity comprises:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative

receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the mammal has been exposed to a test compound that is an inhibitor of tyrosine kinase.

**[0070]** In an other embodiment, the invention includes a method for measuring the level of exposure in a mammal to a test compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens

trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA measured in (c), compared to the level of protein and/or mRNA in step (a) is indicative of the level of exposure in the mammal to the test compound that inhibits tyrosine kinase activity.

**[0071]** Alternatively, a method for measuring the level of exposure in a mammal to a test compound that inhibits tyrosine kinase activity comprises:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase

precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, is indicative of the level of exposure in the mammal to the test compound that inhibits tyrosine kinase activity.

**[0072]** In another embodiment, the invention includes a method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1,

GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that the mammal is responding to the compound that inhibits tyrosine kinase activity.

**[0073]** Alternatively, a method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity comprises:

(a) exposing the mammal to the compound; and

(b) following the exposing step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic



transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said compound, indicates that the mammal is responding to the compound that inhibits tyrosine kinase.

**[0074]** The term “responding” encompasses responding by way of a biological and cellular response, as well as a clinical response (such as improved symptoms, a therapeutic effect or an adverse event), in a mammal.

**[0075]** In another embodiment, the invention includes a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases, wherein the method for identifying the mammal comprises:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation

initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) exposing the mammal to at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases.

**[0076]** In another embodiment, the invention includes a method for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases, wherein the method for testing or predicting comprises:

(a) measuring in a mammal with cancer the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) measuring in a same type of mammal without cancer the level of at least one of the same proteins and/or mRNA transcripts measured in step (a);

(c) comparing levels of said proteins and/or mRNA transcripts measured in (a) and (b);

wherein a difference in the level of said protein and/or mRNA in the mammal with cancer as measured in step (a), compared to the level of said protein and/or mRNA in the

mammal without cancer as measured in step (b), indicates that the mammal will respond therapeutically to at least one inhibitor of VEGFR and/or PDGFR tyrosine kinases.

**[0077]** As used throughout the specification, the term “respond therapeutically” refers to the alleviation or abrogation of a disease, such as cancer. This term means that the life expectancy of an individual affected with the disease will be increased or that one or more of the symptoms of the disease will be reduced or ameliorated. The term encompasses a reduction in cancerous cell growth or tumor volume. Whether a mammal responds therapeutically can be measured by many methods well known in the art, such as PET imaging.

**[0078]** In another embodiment, the mammal is a human. In other embodiments, the mammal is a rat, mouse, dog, rabbit, pig, sheep, cow, horse, cat, primate, or monkey.

**[0079]** In other embodiments, any of the preceding methods is an in vitro method, and the protein and/or mRNA biomarker is measured in at least one mammalian biological tissue. In other embodiments, the protein and/or mRNA biomarker is measured in at least one biological fluid, including but not limited to whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine and saliva. In other embodiments, the protein and/or mRNA biomarker is measured in at least one biological tissue including but not limited to buccal mucosa tissue, skin, hair follicles, tumor tissue and bone marrow.

**[0080]** In yet other embodiments, the methods of the invention are carried out on mammals who have cancer. The cancer can be, for example, but is not limited to, prostate cancer, colorectal cancer (CRC), thyroid cancer, an advanced solid malignancy, pancreatic cancer, breast cancer, parotid cancer, synovial cell cancer or sarcoma, gastrointestinal stromal tumor (GIST), laryngeal cancer, testicular cancer, leiomyosarcoma, rectal cancer, gall-bladder cancer, hepatocellular cancer, melanoma, ovary cancer, lung cancer, colon cancer, renal cell carcinoma, sarcoma, retroperitoneal sarcoma, pelvis sarcoma, uterine cancer, pelvic angiosarcoma, pleural mesothelioma, neuroendocrine cancer, bronchial adenocarcinoma, head and neck cancer and/or thymic cancer.

**[0081]** In other embodiments, any of the preceding methods also comprise a step wherein the mammal is also exposed to a cancer chemotherapeutic agent before, during and/or after exposure to the compound that inhibits tyrosine kinase activity.

**[0082]** Other embodiments also include any of the preceding methods, wherein the “difference” refers to an increase in the level of at least one of the following protein(s) and/or

mRNA transcript(s): PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGR heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), histone H2B, human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ephrin receptor EphB4, OB-cadherin 1, phosphoinositol 3-kinase p85 subunit, mucin 1 and gelsolin, as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0083]** Other embodiments also include any of the proceeding methods wherein the mammal has at least one of prostate cancer, colon cancer, thyroid cancer and an advance solid malignancy, and wherein the “difference” refers to an increase in the level of VEGF protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of VEGF protein and/or mRNA transcript as measured before exposure to the compound.

**[0084]** Other embodiments also include any of the proceeding methods wherein the mammal has colon or colorectal cancer, and wherein the “difference” refers to an increase in the level of at least one of VEGF, MMP-9, lactoferrin, lipocalin-2, and/or CD24 antigen protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0085]** Other embodiments also include any of the proceeding methods wherein the mammal has at least one of synovial sarcoma, rectal cancer, gall-bladder cancer,

hepatocellular cancer, melanoma, breast cancer, ovary cancer, small cell lung cancer, colon cancer, renal cell carcinoma, sarcoma, retroperitoneal sarcoma, pelvis sarcoma, parotid cancer, uterine cancer, pelvic angiosarcoma, colorectal cancer and gastrointestinal stromal tumor (GIST), and wherein the “difference” refers to an increase in the level of at least one of VEGF, PLGF and VEGF/PLGF heterodimers protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0086]** Other embodiments also include any of the preceding methods wherein the mammal has an advanced solid malignancy, and wherein the “difference” refers to an increase in the level of VEGF and/or MMP-9 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0087]** Other embodiments also include any of the preceding methods wherein the mammal has at least one of pancreatic cancer, synovial sarcoma, colon cancer, non-small cell lung cancer (NSCLC), rectal cancer, pelvis sarcoma, and sarcoma and/or bronchial adenocarcinoma, and wherein the “difference” refers to an increase in the level of at least one of MIG, IP-10 and I-TAC protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0088]** Other embodiments also include any of the preceding methods wherein the mammal has thyroid cancer, and wherein the “difference” refers to an increase in the level of at least one of VEGF, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), histone H2b and human RLIP76 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0089]** Other embodiments also include any of the proceeding methods wherein the mammal has pancreatic cancer, and wherein the “difference” refers to an increase in the level of at least one of eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, and human MHC class II lymphocyte antigen (HLA-DP) beta chain protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0090]** Other embodiments also include any of the proceeding methods wherein the mammal has breast cancer, and wherein the “difference” refers to an increase in the level of at least one of human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, and human MHC class II lymphocyte antigen (HLA-DP) beta chain protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0091]** Other embodiments also include any of the proceeding methods wherein the mammal has prostate cancer, and wherein the “difference” refers to an increase in the level of at least one of VEGF, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, and human MHC class II lymphocyte antigen (HLA-DP) beta chain protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0092]** Other embodiments also include any of the proceeding methods wherein the mammal has parotid cancer, and wherein the “difference” refers to an increase in the level of at least one of Homo sapiens thymosin beta-10 gene, Homo sapiens MAP kinase kinase 3

(MKK3) and histone H2B member R protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0093]** Other embodiments also include any of the proceeding methods wherein the mammal has synovial cell cancer, and wherein the “difference” refers to an increase in the level of human RLIP76 protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of human RLIP76 protein and/or mRNA transcript as measured before exposure to the compound.

**[0094]** Other embodiments also include any of the proceeding methods, wherein the “difference” refers to a decrease in the level of at least one of the following protein(s) and/or mRNA transcript(s): ITIH4, PAI-1, soluble VEGF receptor 2 (sVEGFR2), Homo sapiens thymosin beta-10 gene, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, human MHC class II lymphocyte antigen (HLA-DP), human KIAA0195, human beta-tubulin class III isotype (beta-3), Homo sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78, MPIF-1, MMP7, MIG, cdc2 related protein kinase, and phosphoinositol 3-kinase p110 subunit, as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0095]** Other embodiments also include any of the proceeding methods wherein the mammal has is at least one of breast cancer, prostate cancer and thyroid cancer, and wherein the “difference” refers to a decrease in the level of ITIH4 protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of ITIH4 protein and/or mRNA transcript as measured before exposure to the compound.



**[0096]** Other embodiments also include any of the proceeding methods wherein the mammal has is at least one of synovial sarcoma, rectal cancer, gall-bladder cancer, hepatocellular cancer, melanoma, breast cancer, ovary cancer, small cell lung cancer, melanoma, colon cancer, renal cell carcinoma, non-small cell lung cancer (NSCLC), sarcoma, retroperitoneal sarcoma, pelvis sarcoma, squamous cell carcinoma parotid cancer, bronchial adenocarcinoma, uterine cancer, pelvic angiosarcoma, pleural mesothelioma, colorectal cancer (CRC), neuroendocrine cancer, gastrointestinal stromal tumor (GIST), head and neck cancer, thymic cancer and thyroid cancer, and wherein the “difference” refers to a decrease in the level of sVEGFR2 protein and/or mRNA transcript as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of sVEGFR2 protein and/or mRNA transcript as measured before exposure to the compound.

**[0097]** Other embodiments also include any of the proceeding methods wherein the mammal has parotid cancer, and wherein the “difference” refers to a decrease in the level of at least one of Homo sapiens thymosin beta-10 gene, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, human MHC class II lymphocyte antigen (HLA-DP), human beta-tubulin class III isotype (beta-3), and human RLIP76 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0098]** Other embodiments also include any of the proceeding methods wherein the mammal has thyroid cancer, and wherein the “difference” refers to a decrease in the level of at least one of human KIAA0195, human beta-tubulin class III isotype (beta-3), Homo sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC1 emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B member R, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, and human DNA-binding protein A (dbpA) protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0099]** Other embodiments also include any of the proceeding methods wherein the mammal has pancreatic cancer, and wherein the “difference” refers to a decrease in the level of at least one of human KIAA0195, human beta-tubulin class III isotype (beta-3), Homo

sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC1 emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, and human DNA-binding protein A (dbpA) protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0100]** Other embodiments also include any of the proceeding methods wherein the mammal has prostate cancer, and wherein the “difference” refers to a decrease in the level of at least one of human beta-tubulin class III isotype (beta-3), Homo sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC1 emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, and human DNA-binding protein A (dbpA) protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0101]** Other embodiments also include any of the proceeding methods wherein the mammal has breast cancer, and wherein the “difference” refers to a decrease in the level of at least one of human KIAA0195, Homo sapiens trans-golgi network glycoprotein 48, histone H2B and human RLIP76 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

**[0102]** In another embodiment, the invention also includes a kit comprising:

(a) antibody and/or nucleic acid for detecting the presence of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic

ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; and

(b) instructions for determining whether or not a mammal will respond therapeutically to a method of treating cancer comprising administering a compound that inhibits tyrosine kinase activity.

**[0103]** In another embodiment, the invention also includes the preceding kit, wherein the instructions comprise the steps of:

(i) measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens

cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(ii) exposing the mammal to a compound that inhibits tyrosine kinase activity; and

(iii) following the exposing step of (ii), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts for such proteins measured in step (i);

**[0104]** wherein a difference in the level of said proteins and/or mRNA transcripts measured in (iii), compared to the level of proteins and or mRNA transcripts measured in step (i) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering the compound that inhibits tyrosine kinase activity.

**[0105]** In another embodiment, the invention also includes a method for testing or predicting whether a mammal will experience an adverse event in response to a method of treating cancer comprising administering a tyrosine kinase inhibitor, wherein the method for testing or predicting comprises:

(a) measuring in the mammal the level of IL-6 or C-reactive protein (CRP) protein and/or mRNA transcript for such protein and/or gene before administering the tyrosine kinase inhibitor;

(b) measuring in the mammal the level of IL-6 or CRP protein and/or mRNA transcript for such protein and/or gene after administering the tyrosine kinase inhibitor;

(c) comparing levels of said IL-6 or CRP protein and/or mRNA transcript measured in (a) and (b);

wherein a level of two-fold or greater of said protein and/or mRNA transcript as measured in step (b), compared to the level of said protein and/or mRNA transcript as measured in step (a), indicates that the mammal will experience fatigue in response to the method of treating cancer comprising administering the tyrosine kinase inhibitor.

**[0106]** As used in the specification, the term “adverse event” refers to a physiological effect in a mammal, such as fatigue or other side effect, that is severe enough to warrant altering, reducing or eliminating the mammal’s exposure to a particular tyrosine kinase inhibitor. Exposure or administration can be altered, reduced or eliminated in terms of the amount or dosage of the tyrosine kinase inhibitor, as well as length of time and/or frequency of exposure. A determination as to whether a particular physiological effect is severe enough to be considered “an adverse event” falls within the judgment of those skilled in the art, such as a laboratory scientist, veterinarian or medical practitioner.

## **C. Further Embodiments of the Novel Methods**

### **1. Measurement of Protein and mRNA**

**[0107]** In other embodiments, the novel methods of Section B are carried out so that the step where the mammal is exposed to test compound includes administration of at least one dose of test compound, or at least two doses, or at least 5 doses or at least 10 doses, up to at least 55 or 56 doses. In certain embodiments, these doses are administered during a period of 4 hours, 6 hours, or 24 hours to about 100 days. In further embodiments, the doses are administered over a period of 24 hours, 2 days, or 28 days. In other embodiments, two doses are administered per every 24 hours, and in other embodiments, the doses are administered about every 12 hours. It will be understood by those of skill in the art that the administration of test compound, according to the exposure steps of the methods of Section B, can be varied to suit individual needs of the mammal being treated, the compound being administered, the method of administration and the disease being treated. For example, in a typical dosing regimen, the patient receives one dose per day of test compound, for a number of days, such

as about 28 or about 56 days. In other dosing regimens, the test compound is administered about once per day, twice per week, or once per week.

**[0108]** The measurement of protein and/or RNA, following the exposure step in the methods of Section B, can be carried out on a sample from the mammal taken about 4 or 6 hours following the first dose (exposure) of the mammal to test compound. In other embodiments, this measurement is carried out on a sample taken 12 hours, 1 day, 2 days, up to about 100 days, after the first dose (exposure) of the mammal to test compound. In other embodiments, the protein and/or mRNA measurements are taken from samples from the mammals 4 or 6 hours after the first dose of test compound or 24 hours after the first dose of test compound, or 15 or 28 days after the first dose of test compound. Typically, dosing of test compound will be periodic between the first and last dose of test compound that precedes the sample taken for measurement of biomarker protein and/or mRNA. For example, the test compound is administered once a day, every day for 28 days. Typically, the mammal sample taken (for measurement of biomarker protein and/or mRNA) will be taken shortly following the most recent dose of test compound, for example within 24 of the most recent dose of test compound.

**[0109]** In other embodiments, the methods of Section B are carried out so that the measurement of protein and/or mRNA is carried out on a mammalian tissue selected from biological fluids, including but not limited to the group of whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine, saliva, and other tissues including but not limited to buccal mucosa tissue, skin, hair follicles, tumor tissue, bone marrow.

**[0110]** In other embodiments, the methods of Section B are carried out on a mammal that is further exposed to other chemotherapeutic agents, including but not limited to 5-fluoro-uracil (5-FU), leucovorin, CPT11, aromasin, taxol, paclitaxel, other “standard of care” agents used in patients, COX-2 inhibitors (such as celecoxib), and other tyrosine kinase inhibitors. Such exposure to a cancer chemotherapeutic agent can be before, during and/or after exposure to test compound.

**[0111]** In other embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least about 10% or 15% or 20% or 25% or 30% or 35% or 50% or 75% or 100%. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least

25%. In other embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least 2-, 3-, 5-, 10-, 15- or 24-fold. In still further embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least 1.3-, 1.4-, 1.5-, 1.6-, 1.7-, 2.0-, 2.1-, 2.2-, 2.3-, 2.5-, 3.0-, 3.5-, 4.0-, 4.2-, 4.5-, 5.0-, 5.5-, 6.0-, 6.1-, 6.5-, 7.0-, 7.3-, 10.0-, 15.0-, 19.0- or 24-fold. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is an increase of at least about 1.7- or 2.0-fold.

**[0112]** In other embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least about 10% or 15% or 20% or 25% or 30% or 35% or 50% or 75% or 100%. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least about 25%. In still further embodiments, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least 1.3-, 1.4-, 1.5-, 1.6-, 1.7-, 2.0-, 2.1-, 2.2-, 2.3-, 2.5-, 3.0-, 3.5- or 3.7-fold. In another embodiment, the difference in the level of protein or mRNA measured in the methods of Sections B is a decrease of at least about 1.7- or 2.0-fold.

**[0113]** To quantify the protein and/or mRNA measured in the novel methods of Section B, methods well known to the skilled artisan are used. For example, quantification of protein can be carried out using methods such as ELISA, 2-dimensional SDS PAGE, Western Blot, immunoprecipitation, immunohistochemistry, fluorescence activated cell sorting (FACS), flow cytometry. Quantification of mRNA is measured using methods such as PCR, array hybridization, Northern blot, in-situ hybridization, dot-blot, Taqman, RNase protection assay.

**[0114]** In further embodiments of the invention, the methods of Section B are carried out so that the level of at least two, or at least three, or at least four, or at least five, or at least 6, or at least seven or at least eight, or at least nine, up to 87 of the biomarkers are measured in a mammal. In other embodiments, the methods of Section B comprise measuring the level of at least two, up to 66 biomarkers of Section B that are increased upon exposure of a mammal to a compound that inhibits tyrosine kinase. In other embodiments, the methods of Section B comprise measuring the level of at least two, up to 39 biomarkers of Section B that are decreased upon exposure of a mammal to a compound that inhibits tyrosine kinase.

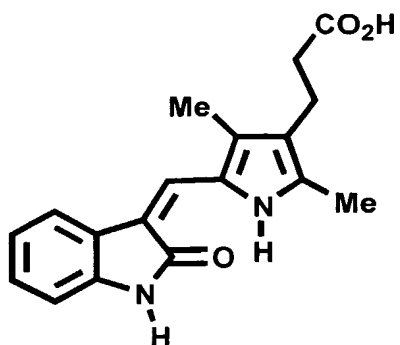
## 2. Tyrosine Kinase and Inhibitors of Tyrosine Kinase

[0115] In certain embodiments, the tyrosine kinases of the novel methods are selected from the group of Flk-1 (KDR), c-kit, FLT1, FLT3, PDGFR-alpha, PDGFR-beta, FGFR-1, FGFR-2 and c-fms/CSF-1 receptor. See, for example, U.S. Pat. No. 6,177,401 (Flk-1), WO 01/45689 (c-kit), GenBank Accession No. NM 002609 (PDGFR-beta), GenBank Accession No. NM 006206 (PDGFR-alpha), GenBank Accession No. NM 023109 (FGFR-1), GenBank Accession No. NM 023028 (FGFR-2) and GenBank Accession No. NP\_005202 (c-fms/CSF-1 receptor).

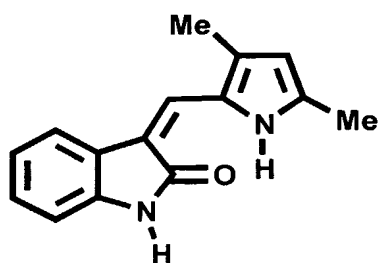
[0116] FLT3 (fms like tyrosine kinase 3) is a member of the class III receptor tyrosine kinases. Those of skill in the art will recognize that FLT3 has also been called "flk2" in the scientific literature. "FLT3" as used herein, refers to a polypeptide having, for example, the sequence set forth in accession number gi|4758396|ref|NP\_004110.1| fms-related tyrosine kinase 3 [Homo sapiens], or gi|544320|sp|P36888|FLT3\_HUMAN FL CYTOKINE RECEPTOR PRECURSOR (TYROSINE-PROTEIN KINASE RECEPTOR FLT3) (STEM CELL TYROSINE KINASE 1) (STK-1) (CD135 ANTIGEN), or gi|409573|gb|AAA18947.1| (U02687) serine/threonine protein kinase [Homo sapiens]. Corresponding mRNA accessions for the first two sequences are gi|4758395|ref|NM\_004119.1| Homo sapiens fms-related tyrosine kinase 3 (FLT3), mRNA gi|406322|emb|Z26652.1|HSFLT3RTK H.sapiens FLT3 mRNA for FLT3 receptor tyrosine kinase.

[0117] In other embodiments, the test compound is an inhibitor of VEGF-mediated signal transduction. In further embodiments, the test compound is an inhibitor of VEGF-mediated tyrosine phosphorylation of a protein kinase, such as Flk-1. In other embodiments, the test compound is an indolinone compound. In another embodiment, the test compound is a compound of Formula I. These, and other exemplary tyrosine kinase inhibitors, are shown below. The skilled artisan will recognize that the novel methods of the invention can be used to test any tyrosine kinase inhibitor, in addition to those listed below.





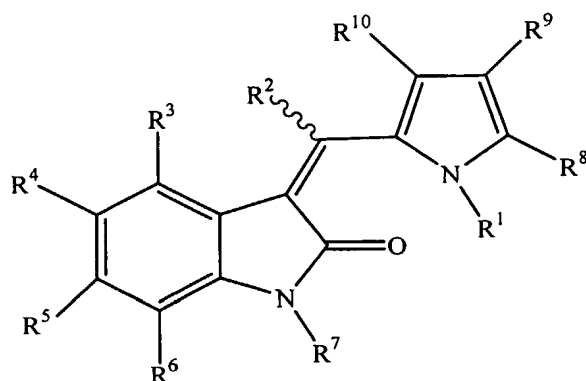
[0118] Compound A (SU6668): 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid.



[0119] Compound B (SU5416): 3-(3,5-dimethyl-1H-pyrrol-2-ylmethylene)-1,3-dihydro-indol-2-one.

[0120]

A pyrrole substituted 2-indolinone having the formula:



wherein:

$R^1$ ,  $R^2$  and  $R^7$  are hydrogen;

$R^3$ ,  $R^4$ ,  $R^5$ , and  $R^6$  are independently selected from the group consisting of hydrogen, hydroxy, halo, unsubstituted lower alkyl, lower alkyl substituted with a carboxylic acid, unsubstituted lower alkoxy, carboxylic acid, unsubstituted aryl, aryl substituted with one or more unsubstituted lower alkyl alkoxy, and morpholino;

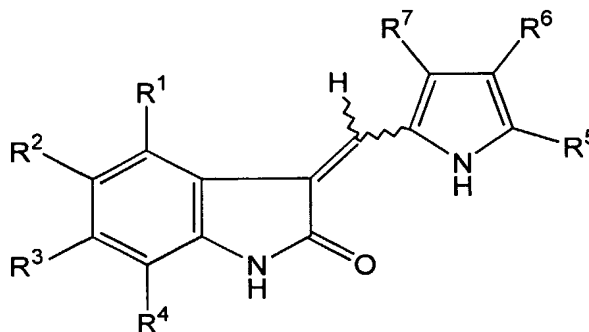
$R^8$  is unsubstituted lower alkyl;

$R^9$  is  $-(CH_2)(CH_2)C(=O)OH$ ; and

$R^{10}$  is unsubstituted lower alkyl.

**[0121]**

A compound having the formula:



wherein:

$R^1$  is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy,  $-(CO)R^{15}$ ,  $-NR^{13}R^{14}$ ,  $-(CH_2)_rR^{16}$  and  $-C(O)NR^8R^9$ ;

$R^2$  is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano,  $-NR^{13}R^{14}$ ,  $-NR^{13}C(O)R^{14}$ ,  $-C(O)R^{15}$ , aryl, heteroaryl, and  $-S(O)_2NR^{13}R^{14}$ ;

$R^3$  is selected from the group consisting of hydrogen, halogen, alkyl, trihalomethyl, hydroxy, alkoxy,  $-(CO)R^{15}$ ,  $-NR^{13}R^{14}$ , aryl, heteroaryl,  $-NR^{13}S(O)_2R^{14}$ ,  $-S(O)_2NR^{13}R^{14}$ ,

$-NR^{13}C(O)R^{14}$ ,

$-NR^{13}C(O)OR^{14}$  and  $-SO_2R^{20}$  (wherein  $R^{20}$  is alkyl, aryl, aralkyl, heteroaryl and

heteroaralkyl);

$R^4$  is selected from the group consisting of hydrogen, halogen, alkyl, hydroxy, alkoxy and  $-NR^{13}R^{14}$ ;

$R^5$  is selected from the group consisting of hydrogen, alkyl and  $-C(O)R^{10}$ ;

$R^6$  is selected from the group consisting of hydrogen, alkyl and  $-C(O)R^{10}$ ;

$R^7$  is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl,  $-C(O)R^{17}$  and  $-C(O)R^{10}$ ; or

$R^6$  and  $R^7$  may combine to form a group selected from the group consisting of  $-(CH_2)_4-$ ,  $-(CH_2)_5-$  and  $-(CH_2)_6-$ ;

with the proviso that at least one of  $R^5$ ,  $R^6$  or  $R^7$  must be  $-C(O)R^{10}$ ;

$R^8$  and  $R^9$  are independently selected from the group consisting of hydrogen, alkyl and aryl;

$R^{10}$  is selected from the group consisting of hydroxy, alkoxy, aryloxy, - $N(R^{11})(CH_2)_nR^{12}$ , and  $-NR^{13}R^{14}$ ;

$R^{11}$  is selected from the group consisting of hydrogen and alkyl;

$R^{12}$  is selected from the group consisting of  $-NR^{13}R^{14}$ , hydroxy,  $-C(O)R^{15}$ , aryl, heteroaryl,  $-N^+(O^-)R^{13}R^{14}$ ,  $-N(OH)R^{13}$ , and  $-NHC(O)R^a$  (wherein  $R^a$  is unsubstituted alkyl, haloalkyl, or aralkyl);

$R^{13}$  and  $R^{14}$  are independently selected from the group consisting of hydrogen, alkyl, lower alkyl substituted with hydroxyalkylamino, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

$R^{13}$  and  $R^{14}$  may combine to form a heterocyclo group;

$R^{15}$  is selected from the group consisting of hydrogen, hydroxy, alkoxy and aryloxy;

$R^{16}$  is selected from the group consisting of hydroxy,

$-C(O)R^{15}$ ,  $-NR^{13}R^{14}$  and  $-C(O)NR^{13}R^{14}$ ;

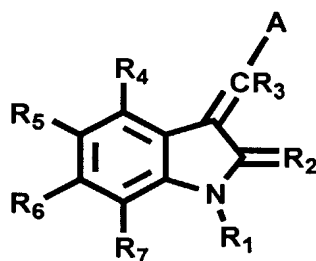
$R^{17}$  is selected from the group consisting of alkyl, cycloalkyl, aryl and heteroaryl;

$R^{20}$  is alkyl, aryl, aralkyl or heteroaryl; and

$n$  and  $r$  are independently 1, 2, 3, or 4;

or a pharmaceutically acceptable salt thereof.

[0122] A compound having the formula:



wherein:

$R_1$  is H;

$R_2$  is O or S;

$R_3$  is hydrogen;

R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>7</sub> are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO<sub>2</sub>NRR', SO<sub>3</sub>R, SR, NO<sub>2</sub>, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>R, and CONRR';

A is a five membered heteroaryl ring selected from the group consisting of thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, optionally substituted at one or more positions with alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO<sub>2</sub>NRR', SO<sub>3</sub>R, SR, NO<sub>2</sub>, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>R or CONRR';

n is 0-3;

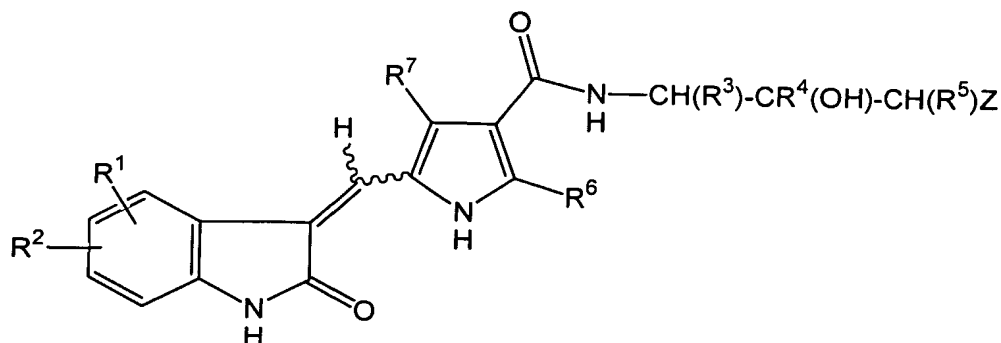
R is H, alkyl or aryl; and

R' is H, alkyl or aryl;

or a pharmaceutically acceptable salt thereof.

**[0123]**

A compound having the formula:



wherein:

$R^1$  is selected from the group consisting of hydrogen, halo, alkyl, haloalkoxy, cycloalkyl, heteroalicyclic, hydroxy, alkoxy,  $-C(O)R^8$ ,  $-NR^9R^{10}$  and  $-C(O)NR^{12}R^{13}$ ;

$R^2$  is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano,  $-NR^9R^{10}$ ,  $-NR^9C(O)R^{10}$ ,  $-C(O)R^8$ ,  $-S(O)_2NR^9R^{10}$  and  $-SO_2R^{14}$  (wherein  $R^{14}$  is alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl);

$R^3$ ,  $R^4$  and  $R^5$  are independently hydrogen or alkyl;

$Z$  is aryl, heteroaryl, heterocycle, or  $-NR^{15}R^{16}$  wherein  $R^{15}$  and  $R^{16}$  are independently hydrogen or alkyl; or  $R^{15}$  and  $R^{16}$  together with the nitrogen atom to which they are attached from a heterocycloamino group;

$R^6$  is selected from the group consisting of hydrogen or alkyl;

$R^7$  is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and  $-C(O)R^{17}$  as defined below;

$R^8$  is selected from the group consisting of hydroxy, alkoxy and aryloxy;

$R^9$  and  $R^{10}$  are independently selected from the group consisting of hydrogen, alkyl, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

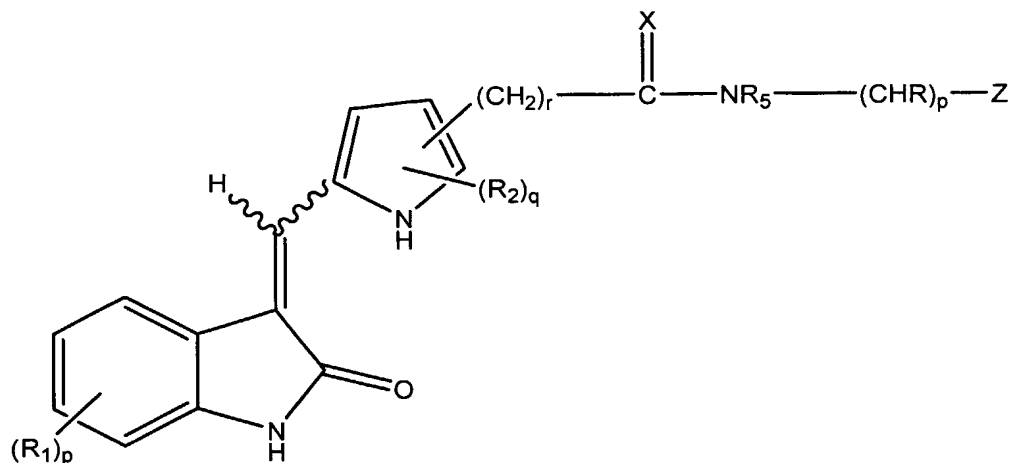
$R^9$  and  $R^{10}$  combine to form a heterocycloamino group;

$R^{12}$  and  $R^{13}$  are independently selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, and aryl; or  $R^{12}$  and  $R^{13}$  together with the nitrogen atom to which they are attached form a heterocycloamino;

$R^{17}$  is selected from the group consisting of alkyl, cycloalkyl, aryl, hydroxy and heteroaryl;

or a pharmaceutically acceptable salt thereof.

[0124] In other embodiments of the invention, a mammal is exposed to a compound of Formula I:



(I),

wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each  $R_1$  is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy,  $-C(O)-R_8$ ,  $-NR_9R_{10}$ ,  $-NR_9C(O)-R_{12}$  and  $-C(O)NR_9R_{10}$ ;

each  $R_2$  is independently selected from the group consisting of alkyl, aryl, heteroaryl,  $-C(O)-R_8$ , and  $SO_2R''$ , where  $R''$  is alkyl, aryl, heteroaryl,  $NR_9N_{10}$  or alkoxy;

each  $R_5$  is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy,  $-C(O)-R_8$  and  $(CHR)_rR_{11}$ ;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

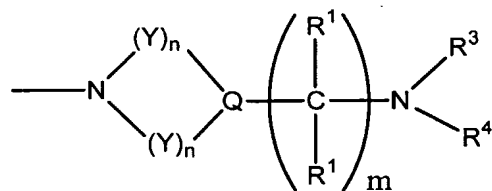
$R_8$  is selected from the group consisting of  $-OH$ , alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

$R_9$  and  $R_{10}$  are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or  $R_9$  and  $R_{10}$  together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

$R_{11}$  is selected from the group consisting of  $-OH$ , amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

$R_{12}$  is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH, O-alkyl, or  $-NR_3R_4$ , where  $R_3$  and  $R_4$  are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or  $R_3$  and  $R_4$  may combine with N to form a ring where the ring atoms are selected from the group consisting of  $CH_2$ , N, O and S or



wherein Y is independently  $CH_2$ , O, N or S,

Q is C or N;

n is independently 0-4; and

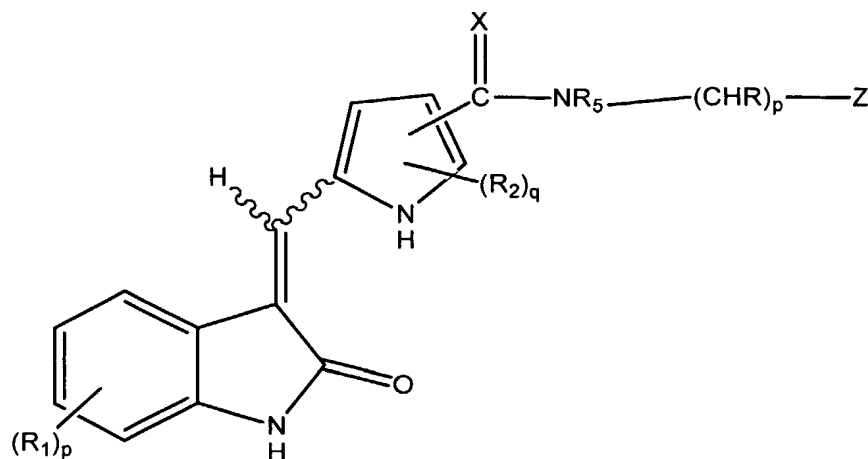
m is 0-3;

or a pharmaceutically acceptable salt thereof.

**[0125]**



In another embodiment, a mammal is exposed to a compound of Formula II:



(II),

wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each  $R_1$  is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy,  $-C(O)-R_8$ ,  $-NR_9R_{10}$ ,  $-NR_9C(O)-R_{12}$  and  $-C(O)NR_9R_{10}$ ;

each  $R_2$  is independently selected from the group consisting of alkyl, aryl, heteroaryl,  $-C(O)-R_8$ , and  $SO_2R''$ , where  $R''$  is alkyl, aryl, heteroaryl,  $NR_9N_{10}$  or alkoxy;

each  $R_5$  is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy,  $-C(O)-R_8$  and  $(CHR)_rR_{11}$ ;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

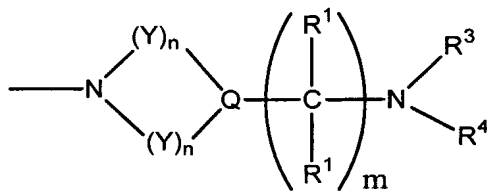
$R_8$  is selected from the group consisting of  $-OH$ , alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

$R_9$  and  $R_{10}$  are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or  $R_9$  and  $R_{10}$  together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

$R_{11}$  is selected from the group consisting of  $-OH$ , amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

$R_{12}$  is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is  $OH$ ,  $O$ -alkyl, or  $-NR_3R_4$ , where  $R_3$  and  $R_4$  are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or  $R_3$  and  $R_4$  may combine with N to form a ring where the ring atoms are selected from the group consisting of  $CH_2$ , N, O and S or



wherein Y is independently  $CH_2$ , O, N or S,

Q is C or N;

n is independently 0-4; and

m is 0-3;

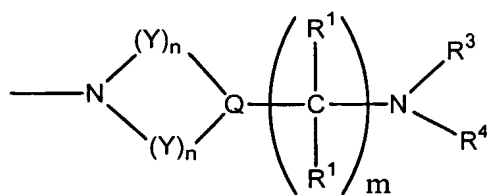
or a pharmaceutically acceptable salt thereof.

**[0126]** In another embodiment of the invention, a mammal is exposed to a compound of Formula I or II, wherein  $R_1$  is halo (e.g., F and Cl) and Z is  $-NR_3R_4$  wherein  $R_3$  and  $R_4$  are independently H or alkyl.

**[0127]** In another embodiment, Z of Formula I or II is  $-NR_3R_4$ , wherein  $R_3$  and  $R_4$  form a morpholine ring.

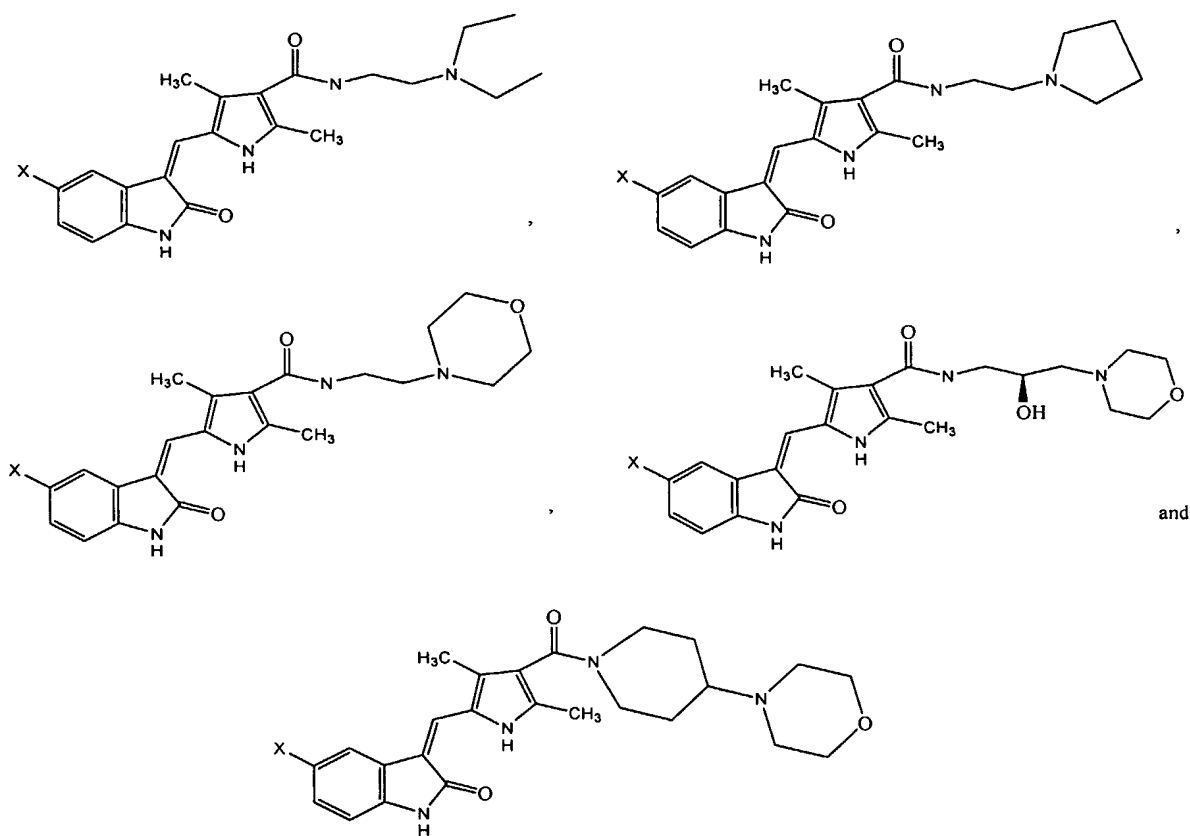
**[0128]**

In another embodiment, Z of Formula I or II is:



wherein each Y is CH<sub>2</sub>, each n is 2, m is 0 and R<sub>3</sub> and R<sub>4</sub> form a morpholine ring.

**[0129]** In another embodiment of the invention, a mammal is exposed to a compound selected from the group consisting of



wherein X is F, Cl, I or Br; or a pharmaceutically acceptable salt thereof. In another embodiment, X is F.

**[0130]** In another embodiment of the invention, a mammal is exposed to a compound of Formula I selected from the group consisting of:

5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (Compound 1);

5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide (Compound 2);

5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide (Compound 3);

(S)-5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 4);

(R)-5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 5);

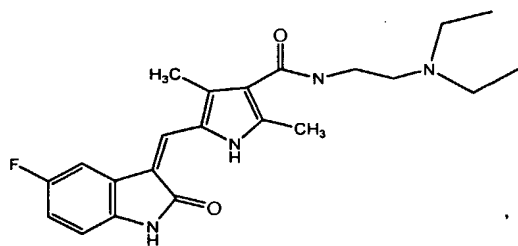
5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 6);

5-(5-Chloro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-morpholin-4-yl-propyl)-amide (Compound 7);

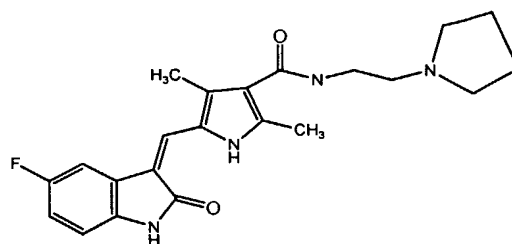
5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-ethylamino-ethyl)-amide (Compound 8);

3-[3,5-dimethyl-4-(4-morpholin-4-yl-piperidine-1-carbonyl)-1H-pyrrol-2-methylene]-5-fluoro-1,3-dihydro-indol-2-one (Compound 9).

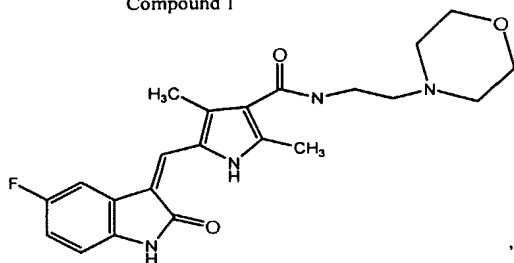
**[0131]** The above compounds are shown below:



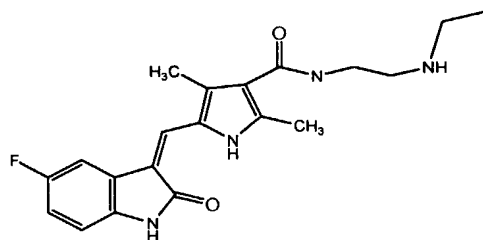
Compound 1



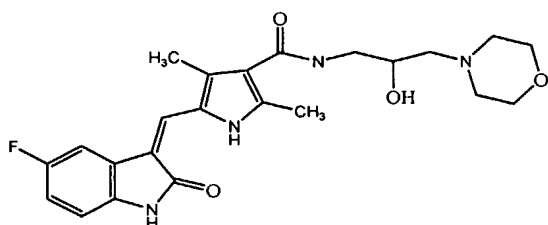
Compound 2



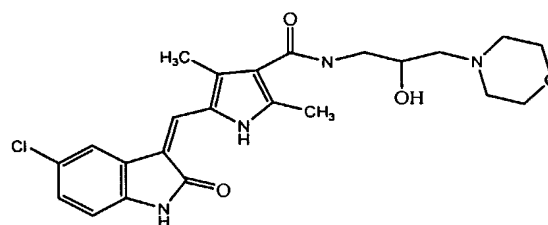
Compound 3



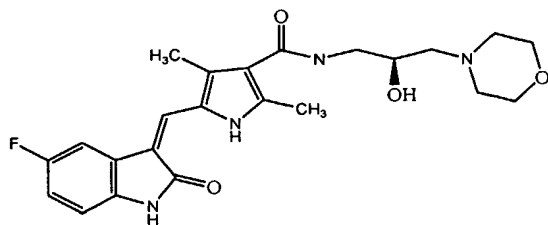
Compound 8



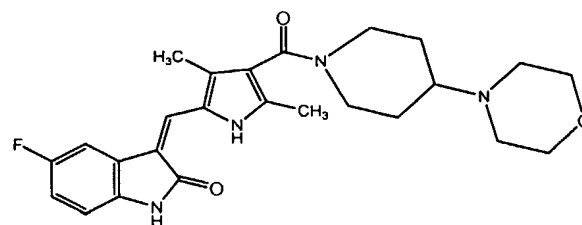
Compound 6



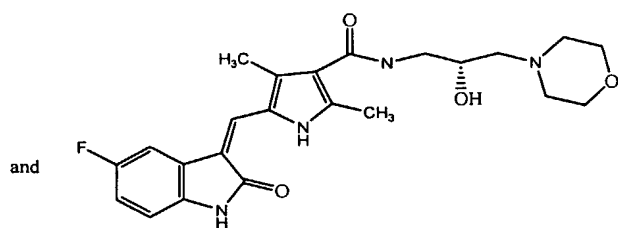
Compound 7



Compound 4



Compound 9



Compound 5

**[0132]** To clearly set forth the compounds of Formula I, Formula II and other compounds of the formulas described herein, useful in the inventive method, the following definitions are provided.

[0133] "Alkyl" refers to a saturated aliphatic hydrocarbon radical including straight chain and branched chain groups of 1 to 20 carbon atoms (whenever a numerical range; e.g. "1-20", is stated herein, it means that the group, in this case the alkyl group, may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). Alkyl groups containing from 1 to 4 carbon atoms are referred to as lower alkyl groups. When said lower alkyl groups lack substituents, they are referred to as unsubstituted lower alkyl groups. More preferably, an alkyl group is a medium size alkyl having 1 to 10 carbon atoms e.g., methyl, ethyl, propyl, 2-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, and the like. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms e.g., methyl, ethyl, propyl, 2-propyl, n-butyl, iso-butyl, or tert-butyl, and the like. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, more preferably one to three, even more preferably one or two substituent(s) independently selected from the group consisting of halo, hydroxy, unsubstituted lower alkoxy, aryl optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, aryloxy optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 6-member heteroaryl having from 1 to 3 nitrogen atoms in the ring, the carbons in the ring being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5-member heteroaryl having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and the nitrogen atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5- or 6-member heterocyclic group having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen (if present) atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, mercapto, (unsubstituted lower alkyl)thio, arylthio optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or alkoxy groups, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, RS(O)<sub>2</sub>-, -C(O)OR,

RC(O)O-, and  $-NR_{13}R_{14}$ , wherein  $R_{13}$  and  $R_{14}$  are independently selected from the group consisting of hydrogen, unsubstituted lower alkyl, trihalomethyl, cycloalkyl, heterocyclic and aryl optionally substituted with one or more, groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups.

**[0134]** Preferably, the alkyl group is substituted with one or two substituents independently selected from the group consisting of hydroxy, 5- or 6-member heterocyclic group having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen (if present) atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5-member heteroaryl having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and the nitrogen atoms in the group being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 6-member heteroaryl having from 1 to 3 nitrogen atoms in the ring, the carbons in the ring being optionally substituted with one or more groups, preferably one, two or three groups which are independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, or  $-NR_{13}R_{14}$ , wherein  $R_{13}$  and  $R_{14}$  are independently selected from the group consisting of hydrogen and alkyl. Even more preferably the alkyl group is substituted with one or two substituents which are independently of each other hydroxy, dimethylamino, ethylamino, diethylamino, dipropylamino, pyrrolidino, piperidino, morpholino, piperazino, 4-lower alkylpiperazino, phenyl, imidazolyl, pyridinyl, pyridazinyl, pyrimidinyl, oxazolyl, triazinyl, and the like.

**[0135]** "Cycloalkyl" refers to a 3 to 8 member all-carbon monocyclic ring, an all-carbon 5-member/6-member or 6-member/6-member fused bicyclic ring or a multicyclic fused ring (a "fused" ring system means that each ring in the system shares an adjacent pair of carbon atoms with each other ring in the system) group wherein one or more of the rings may contain one or more double bonds but none of the rings has a completely conjugated pi-electron system.

**[0136]** Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexadiene, adamantane, cycloheptane, cycloheptatriene, and the like. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more, more

preferably one or two substituents, independently selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, aryl optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, aryloxy optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 6-member heteroaryl having from 1 to 3 nitrogen atoms in the ring, the carbons in the ring being optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5-member heteroaryl having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen atoms of the group being optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, 5- or 6-member heterocyclic group having from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, the carbon and nitrogen (if present) atoms in the group being optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, mercapto, (unsubstituted lower alkyl)thio, arylthio optionally substituted with one or more, preferably one or two groups independently of each other halo, hydroxy, unsubstituted lower alkyl or unsubstituted lower alkoxy groups, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, RS(O)<sub>2</sub>-, -C(O)OR, RC(O)O-, and -NR<sub>13</sub>R<sub>14</sub> are as defined above.

**[0137]** "Alkenyl" refers to a lower alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond. Representative examples include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 1-, 2-, or 3-butenyl, and the like.

**[0138]** "Alkynyl" refers to a lower alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond. Representative examples include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-, 2-, or 3-butynyl, and the like.

**[0139]** "Aryl" refers to an all-carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups of 1 to 12 carbon atoms having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted.



When substituted, the substituted group(s) is preferably one or more, more preferably one, two or three, even more preferably one or two, independently selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, mercapto, (unsubstituted lower alkyl)thio, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, RS(O)<sub>2</sub>-, -C(O)OR, RC(O)O-, and -NR<sub>13</sub>R<sub>14</sub>, with R<sub>13</sub> and R<sub>14</sub> as defined above. Preferably, the aryl group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

**[0140]** "Heteroaryl" refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group of 5 to 12 ring atoms containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of unsubstituted heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, isoquinoline, purine and carbazole. The heteroaryl group may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more, more preferably one, two, or three, even more preferably one or two, independently selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, mercapto, (unsubstituted lower alkyl)thio, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, RS(O)<sub>2</sub>-, -C(O)OR, RC(O)O-, and -NR<sub>13</sub>R<sub>14</sub>, with R<sub>13</sub> and R<sub>14</sub> as defined above. Preferably, the heteroaryl group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

**[0141]** "Heterocyclic" refers to a monocyclic or fused ring group having in the ring(s) of 5 to 9 ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or S(O)<sub>n</sub> (where n is an integer from 0 to 2), the remaining ring atoms being C. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of unsubstituted heterocyclic groups are pyrrolidino, piperidino, piperazino, morpholino, thiomorpholino, homopiperazino, and the like. The heterocyclic ring may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more, more preferably one, two or three, even more preferably one or two, independently selected from the group consisting of unsubstituted

lower alkyl, trihaloalkyl, halo, hydroxy, unsubstituted lower alkoxy, mercapto, (unsubstituted lower alkyl)thio, cyano, acyl, thioacyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, nitro, N-sulfonamido, S-sulfonamido, RS(O)-, RS(O)<sub>2</sub>-, -C(O)OR, RC(O)O-, and -NR<sub>13</sub>R<sub>14</sub>, with R<sub>13</sub> and R<sub>14</sub> as defined above. Preferably, the heterocyclic group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

[0142] Preferably, the heterocyclic group is optionally substituted with one or two substituents independently selected from halo, unsubstituted lower alkyl, trihaloalkyl, hydroxy, mercapto, cyano, N-amido, mono or dialkylamino, carboxy, or N-sulfonamido.

[0143] "Hydroxy" refers to an -OH group.

[0144] "Alkoxy" refers to both an -O-(unsubstituted alkyl) and an -O-(unsubstituted cycloalkyl) group. Representative examples include, but are not limited to, e.g., methoxy, ethoxy, propoxy, butoxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

[0145] "Aryloxy" refers to both an -O-aryl and an -O-heteroaryl group, as defined herein. Representative examples include, but are not limited to, phenoxy, pyridinyloxy, furanyloxy, thienyloxy, pyrimidinyloxy, pyrazinyloxy, and the like, and derivatives thereof.

[0146] "Mercapto" refers to an -SH group.

[0147] "Alkylthio" refers to both an -S-(unsubstituted alkyl) and an -S-(unsubstituted cycloalkyl) group. Representative examples include, but are not limited to, e.g., methylthio, ethylthio, propylthio, butylthio, cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, and the like.

[0148] "Arylthio" refers to both an -S-aryl and an -S-heteroaryl group, as defined herein. Representative examples include, but are not limited to, phenylthio, pyridinylthio, furanylthio, thientylthio, pyrimidinylthio, and the like and derivatives thereof.

[0149] "Acyl" refers to a -C(O)-R" group, where R" is selected from the group consisting of hydrogen, unsubstituted lower alkyl, trihalomethyl, unsubstituted cycloalkyl, aryl optionally substituted with one or more, preferably one, two, or three substituents selected from the group consisting of unsubstituted lower alkyl, trihalomethyl, unsubstituted lower alkoxy, halo and -NR<sub>13</sub>R<sub>14</sub> groups, heteroaryl (bonded through a ring carbon) optionally substituted with one or more, preferably one, two, or three substituents selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, unsubstituted lower alkoxy, halo and -NR<sub>13</sub>R<sub>14</sub> groups and heterocyclic (bonded through a ring carbon)

optionally substituted with one or more, preferably one, two, or three substituents selected from the group consisting of unsubstituted lower alkyl, trihaloalkyl, unsubstituted lower alkoxy, halo and

$-NR_{13}R_{14}$  groups. Representative acyl groups include, but are not limited to, acetyl, trifluoroacetyl, benzoyl, and the like.

**[0150]** "Aldehyde" refers to an acyl group in which R" is hydrogen.

**[0151]** "Thioacyl" refers to a  $-C(S)-R$ " group, with R" as defined herein.

**[0152]** "Ester" refers to a  $-C(O)O-R$ " group with R" as defined herein except that R" cannot be hydrogen.

**[0153]** "Acetyl" group refers to a  $-C(O)CH_3$  group.

**[0154]** "Halo" group refers to fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

**[0155]** "Trihalomethyl" group refers to a  $-CX_3$  group wherein X is a halo group as defined herein.

**[0156]** "Methylenedioxy" refers to a  $-OCH_2O-$  group where the two oxygen atoms are bonded to adjacent carbon atoms.

**[0157]** "Ethylenedioxy" group refers to a  $-OCH_2CH_2O-$  where the two oxygen atoms are bonded to adjacent carbon atoms.

**[0158]** "S-sulfonamido" refers to a  $-S(O)_2NR_{13}R_{14}$  group, with  $R_{13}$  and  $R_{14}$  as defined herein.

**[0159]** "N-sulfonamido" refers to a  $-NR_{13}S(O)_2R$  group, with  $R_{13}$  and R as defined herein.

**[0160]** "O-carbamyl" group refers to a  $-OC(O)NR_{13}R_{14}$  group with  $R_{13}$  and  $R_{14}$  as defined herein.

**[0161]** "N-carbamyl" refers to an  $ROC(O)NR_{14}-$  group, with R and  $R_{14}$  as defined herein.

**[0162]** "O-thiocarbamyl" refers to a  $-OC(S)NR_{13}R_{14}$  group with  $R_{13}$  and  $R_{14}$  as defined herein.

**[0163]** "N-thiocarbamyl" refers to a  $ROC(S)NR_{14}-$  group, with R and  $R_{14}$  as defined herein.

**[0164]** "Amino" refers to an  $-NR_{13}R_{14}$  group, wherein  $R_{13}$  and  $R_{14}$  are both hydrogen.

**[0165]** "C-amido" refers to a  $-C(O)NR_{13}R_{14}$  group with  $R_{13}$  and  $R_{14}$  as defined herein.

[0166] "N-amido" refers to a  $RC(O)NR_{14}$  group, with R and  $R_{14}$  as defined herein.

[0167] "Nitro" refers to a  $-NO_2$  group.

[0168] "Haloalkyl" means an unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above that is substituted with one or more same or different halo atoms, e.g.,  $-CH_2Cl$ ,  $-CF_3$ ,  $-CH_2CF_3$ ,  $-CH_2CCl_3$ , and the like.

[0169] "Aralkyl" means unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above which is substituted with an aryl group as defined above, e.g.,  $-CH_2phenyl$ ,  $-(CH_2)_2phenyl$ ,  $-(CH_2)_3phenyl$ ,  $CH_3CH(CH_3)CH_2phenyl$ , and the like and derivatives thereof.

[0170] "Heteroaralkyl" group means unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above which is substituted with a heteroaryl group, e.g.,  $-CH_2pyridinyl$ ,  $-(CH_2)_2pyrimidinyl$ ,  $-(CH_2)_3imidazolyl$ , and the like, and derivatives thereof.

[0171] "Monoalkylamino" means a radical  $-NHR'$  where  $R'$  is an unsubstituted alkyl or unsubstituted cycloalkyl group as defined above, e.g., methylamino, (1-methylethyl)amino, cyclohexylamino, and the like.

[0172] "Dialkylamino" means a radical  $-NR'R'$  where each  $R'$  is independently an unsubstituted alkyl or unsubstituted cycloalkyl group as defined above, e.g., dimethylamino, diethylamino, (1-methylethyl)-ethylamino, cyclohexylmethylamino, cyclopentylmethylamino, and the like.

[0173] "Cyanoalkyl" means unsubstituted alkyl, preferably unsubstituted lower alkyl as defined above, which is substituted with 1 or 2 cyano groups.

[0174] "Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocycle group optionally substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the heterocycle group is substituted with an alkyl group and situations where the heterocycle group is not substituted with the alkyl group.

[0175] A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or physiologically/pharmaceutically acceptable salts or prodrugs thereof, with other chemical components, such as physiologically/pharmaceutically acceptable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

**[0176]** As used herein, a "physiologically/pharmaceutically acceptable carrier" refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

**[0177]** An "pharmaceutically acceptable excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

**[0178]** As used herein, the term "salt" of a compound of Formula I, II or other formulas or compounds described in this specification refers to those salts which retain the biological effectiveness and properties of the parent compound. Such salts include:

(i) acid addition salt which is obtained by reaction of the free base of the parent compound with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, sulfuric acid, and perchloric acid and the like, or with organic acids such as acetic acid, oxalic acid, (D) or (L) malic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid or malonic acid and the like, preferably hydrochloric acid or (L)-malic acid such as the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid(2-diethylaminoethyl)amide; or

(ii) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

**[0179]** "Method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by, practitioners of the chemical, pharmaceutical, biological, biochemical and medical arts.

**[0180]** "In vivo" refers to procedures performed within a living organism such as, without limitation, a mouse, rat or rabbit.

[0181] "Treat", "treating" and "treatment" refer to a method of alleviating, ameliorating, abrogating or relieving a disease condition and/or any of its attendant symptoms.

[0182] "Patient" refers to any living entity comprised of at least one cell. A living organism can be as simple as, for example, a single eukariotic cell or as complex as a mammal, including a human being.

[0183] "Therapeutically effective amount" refers to that amount of the compound being administered which will prevent, alleviate, ameliorate or relieve to some extent, one or more of the signs or symptoms of the disorder being treated.

## ADMINISTRATION AND PHARMACEUTICAL COMPOSITION

[0184] In another embodiment of the invention, a human patient is exposed or administered a compound of Formula I, Formula II or other formulas or compounds described in this application, or a pharmaceutically acceptable salt thereof. Alternatively, the compounds of Formula I, Formula II or other formulas or compounds described herein can be administered in pharmaceutical compositions in which the foregoing materials are mixed with suitable carriers or excipient(s). Techniques for formulation and administration of drugs may be found in "Remington's Pharmacological Sciences," Mack Publishing Co., Easton, PA., latest edition.

[0185] As used herein, "exposing," "administer" or "administration" refers to the delivery of a compound of Formula I, Formula II or other formulas or compounds described herein or a pharmaceutically acceptable salt thereof or of a pharmaceutical composition containing a compound of Formula I, Formula II or other formulas or compounds described herein or a pharmaceutically acceptable salt thereof of this invention to a mammal.

[0186] Suitable routes of administration may include, without limitation, oral, rectal, transmucosal or intestinal administration or intramuscular, subcutaneous, intramedullary, intrathecal, direct intraventricular, intravenous, intravitreal, intraperitoneal, intranasal, or intraocular injections. The preferred routes of administration are oral and parenteral.

[0187] Furthermore, one administer the compound in a targeted drug delivery system, for example, in a liposome coated with tumor-specific antibody. The liposomes will be targeted to and taken up selectively by the tumor progenitor.

[0188] Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

[0189] Pharmaceutical compositions for use in accordance with the present invention may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[0190] For injection, the compounds of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0191] For oral administration, the compounds can be formulated by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, lozenges, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient. Pharmaceutical preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding other suitable auxiliaries if desired, to obtain tablets or dragee cores. Useful excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol, cellulose preparations such as, for example, maize starch, wheat starch, rice starch and potato starch and other materials such as gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as cross-linked polyvinylpyrrolidone, agar, or alginic acid. A salt such as sodium alginate may also be used.

[0192] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0193] Pharmaceutical compositions which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with a filler such as lactose, a binder such as starch, and/or a lubricant such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. Stabilizers may be added in these formulations, also.

[0194] Pharmaceutical compositions which may also be used include hard gelatin capsules. As a non-limiting example, compound 1 in a capsule oral drug product formulation may be as 50 and 200 mg dose strengths. The two dose strengths are made from the same granules by filling into different size hard gelatin capsules, size 3 for the 50 mg capsule and size 0 for the 200 mg capsule.

[0195] The capsules may be packaged into brown glass or plastic bottles to protect the active compound from light. The containers containing the active compound capsule formulation must be stored at controlled room temperature (15-30°C).

[0196] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray using a pressurized pack or a nebulizer and a suitable propellant, e.g., without limitation, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra- fluoroethane or carbon dioxide. In the case of a pressurized aerosol, the dosage unit may be controlled by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0197] The compounds may also be formulated for parenteral administration, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating materials such as suspending, stabilizing and/or dispersing agents.

[0198] Pharmaceutical compositions for parenteral administration include aqueous solutions of a water soluble form, such as, without limitation, a salt, of the active compound. Additionally, suspensions of the active compounds may be prepared in a lipophilic vehicle. Suitable lipophilic vehicles include fatty oils such as sesame oil, synthetic fatty acid esters such as ethyl oleate and triglycerides, or materials such as liposomes. Aqueous injection



suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers and/or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

**[0199]** Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

**[0200]** The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, using, e.g., conventional suppository bases such as cocoa butter or other glycerides.

**[0201]** In addition to the formulations described previously, the compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. A compound of this invention may be formulated for this route of administration with suitable polymeric or hydrophobic materials (for instance, in an emulsion with a pharmacologically acceptable oil), with ion exchange resins, or as a sparingly soluble derivative such as, without limitation, a sparingly soluble salt.

**[0202]** A non-limiting example of a pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer and an aqueous phase such as the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:D5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of such a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of Polysorbate 80, the fraction size of polyethylene glycol may be varied, other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone, and other sugars or polysaccharides may substitute for dextrose.

**[0203]** Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. In addition, certain organic solvents such as dimethylsulfoxide also may be employed, although often at the cost of greater toxicity.

**[0204]** Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

**[0205]** The pharmaceutical compositions herein also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

**[0206]**

Examples of formulations for use in the present invention are in Tables A-C:

**TABLE A**

| <b>Composition of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide hard gelatin capsules</b> |   |                                     |                                     |                                      |
|---|---|-------------------------------------|-------------------------------------|--------------------------------------|
| <b>Ingredient Name</b>  | <b>Concentration in Granulation (% w/w)</b> | <b>Amount in 50 mg Capsule (mg)</b> | <b>Amount in 75 mg Capsule (mg)</b> | <b>Amount in 200 mg Capsule (mg)</b> |
| <b>API</b>  | <b>65.0</b>                                 | <b>50.0</b>                         | <b>75.0</b>                         | <b>200.0</b>                         |
| <b>Mannitol</b>   | <b>23.5</b>                                 | <b>18.1</b>                         | <b>27.2</b>                         | <b>72.4</b>                          |
| <b>Croscarmellose Sodium<sup>c</sup></b>  | <b>6.0</b>                                  | <b>4.6</b>                          | <b>6.9</b>                          | <b>18.4</b>                          |
| <b>Povidone (K-25)</b>  | <b>5.0</b>                                  | <b>3.8</b>                          | <b>5.7</b>                          | <b>15.2</b>                          |
| <b>Magnesium Stearate</b>   | <b>0.5</b>                                  | <b>0.38</b>                         | <b>0.57</b>                         | <b>1.52</b>                          |
| <b>Capsule</b>  | <b>-</b>                                    | <b>Size 1</b>                       | <b>Size 3</b>                       | <b>Size 0</b>                        |

**TABLE B**

| <b>Composition of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate hard gelatin capsules</b> |   |                                     |
|--|---|-------------------------------------|
| <b>Ingredient Name/Grade</b>   | <b>Concentration in Granulation (% w/w)</b> | <b>Amount in 50 mg Capsule (mg)</b> |
| <b>API</b>   | <b>75.0</b>                                 | <b>66.800<sup>c</sup></b>           |
| <b>Mannitol</b>  | <b>13.5</b>                                 | <b>12.024</b>                       |
| <b>Croscarmellose Sodium<sup>c</sup></b>   | <b>6.0</b>                                  | <b>5.344</b>                        |
| <b>Povidone (K-25)</b>   | <b>5.0</b>                                  | <b>4.453</b>                        |
| <b>Magnesium Stearate</b>  | <b>0.5</b>                                  | <b>1.445</b>                        |
| <b>Capsule</b>   | <b>-</b>                                    | <b>Size 3</b>                       |

TABLE C

| <b>Composition of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate hard gelatin capsules</b> |   |                                     |                                     |                                      |
|--|---|-------------------------------------|-------------------------------------|--------------------------------------|
| <b>Ingredient Name/Grade</b>   | <b>Concentration in Granulation (% w/w)</b> | <b>Amount in 25 mg Capsule (mg)</b> | <b>Amount in 50 mg Capsule (mg)</b> | <b>Amount in 100 mg Capsule (mg)</b> |
| <b>API<sup>a</sup></b>   | <b>40.0</b>                                 | <b>33.400<sup>d</sup></b>           | <b>66.800<sup>c</sup></b>           | <b>200.0<sup>b</sup></b>             |
| <b>Mannitol</b>  | <b>47.5</b>                                 | <b>39.663</b>                       | <b>79.326</b>                       | <b>158.652</b>                       |
| <b>Croscarmellose Sodium<sup>e</sup></b>   | <b>6.0</b>                                  | <b>5.010</b>                        | <b>10.020</b>                       | <b>20.04</b>                         |
| <b>Povidone (K-25)</b>   | <b>5.0</b>                                  | <b>4.175</b>                        | <b>8.350</b>                        | <b>16.700</b>                        |
| <b>Magnesium Stearate</b>  | <b>1.5</b>                                  | <b>1.252</b>                        | <b>2.504</b>                        | <b>5.008</b>                         |
| <b>Capsule</b>   | <b>-</b>                                    | <b>Size 3</b>                       | <b>Size 1</b>                       | <b>Size 0</b>                        |

<sup>a</sup> Drug substance quantity required for the batch will be adjusted to have 100% of labeled strength for capsules. Appropriate adjustment will be made to mannitol quantity to keep the same fill weight for each strength.

<sup>b</sup> Quantity equivalent to 100 mg free base.

<sup>c</sup> Quantity equivalent to 50 mg free base.

<sup>d</sup> Quantity equivalent to 25 mg free base.

<sup>e</sup> Half intragranular half extragranular.

which can be found in U.S. Patent Application Serial No. 10/237,966, filed September 10, 2002, now a provisional application, which is expressly incorporated in its entirety by reference.

[0207] Many of the compounds of Formula I, Formula II or other formulas or compounds described herein may be provided as physiologically acceptable salts wherein the compound may form the negatively or the positively charged species. Examples of salts in which the compound forms the positively charged moiety include, without limitation, quaternary ammonium, salts such as the hydrochloride, sulfate, carbonate, lactate, tartrate, malate, maleate, succinate wherein the nitrogen atom of the quaternary ammonium group is a nitrogen of the selected compound of this invention which has reacted with the appropriate acid. Salts in which a compound of this invention forms the negatively charged species include, without limitation, the sodium, potassium, calcium and magnesium salts formed by the reaction of a carboxylic acid group in the compound with an appropriate base (e.g. sodium hydroxide (NaOH), potassium hydroxide (KOH), Calcium hydroxide (Ca(OH)<sub>2</sub>), etc.).

[0208] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose, *i.e.*, a therapeutically effective amount.

[0209] Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0210] For any compound used in the methods of the invention, the therapeutically effective amount or dose can be estimated initially from cell culture assays. Then, the dosage can be formulated for use in animal models so as to achieve a circulating concentration range that includes the  $IC_{50}$  as determined in cell culture (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of phosphorylation of CSF1R). Such information can then be used to more accurately determine useful doses in humans.

[0211] Toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, by determining the  $IC_{50}$  and the  $LD_{50}$ , wherein the  $LD_{50}$  is the concentration of test compound which achieves a half-maximal inhibition of lethality, for a subject compound. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See *e.g.*, Fingl, et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1).

[0212] Dosage amount and interval may be adjusted individually to provide plasma levels of the active species which are sufficient to maintain the kinase modulating effects. These plasma levels are referred to as minimal effective concentrations (MECs). The MEC will vary for each compound but can be estimated from *in vitro* data, *e.g.*, the concentration necessary to achieve 50-90% inhibition of a kinase may be ascertained using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. HPLC assays or bioassays can be used to determine plasma concentrations.

[0213] Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen that maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

[0214] At present, the therapeutically effective amounts of compounds of Formula I, Formula II or other formulas or compounds described in this application may range from approximately 25 mg/m<sup>2</sup> to 1500 mg/m<sup>2</sup> per day; alternatively about approximately 25 mg/m<sup>2</sup> to 1000 mg/m<sup>2</sup> per day. In another embodiment, the therapeutically effective amounts may range from approximately 25 mg/m<sup>2</sup> to 400 mg/m<sup>2</sup> per day.

[0215] In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration and other procedures known in the art may be employed to determine the correct dosage amount and interval.

[0216] The amount of a composition administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, etc.

[0217] It is contemplated that the inventive method could be used in combination with other therapies, including chemotherapies, radiation therapies and surgical therapies for cancer. For combination therapies and pharmaceutical compositions described herein, the effective amounts of the compound of the invention and of the other agent can be determined by those of ordinary skill in the art, based on the effective amounts for the compounds described herein and those known or described for the other agent. The formulations and route of administration for such therapies and composition can be based on the information described herein for compositions and therapies comprising the compound of the invention as the sole active agent and on information provided for the chemotherapeutic and other agent in combination therewith.

[0218] Although all biomarkers disclosed in this specification are identified by specific sequences (and corresponding SEQ ID NOs), those skilled in the art will recognize that variants and alleles of these sequences also may function as biomarkers. Specific sequences, GenBank accession numbers and SEQ ID NOs in the specification are used to identify exemplary cDNAs, mRNAs and/or proteins of interest, and do not limit the invention to only those particular sequences. The biomarkers of the invention encompass variants and alleles of the disclosed sequences.

**D. EXAMPLES – STUDIES USING COMPOUND A (SU6668)****1. Studies using Compound A – Materials and Methods****ELISAs**

[0219] Reagents for human tissue inhibitor of metalloproteinase 1 (TIMP-1), human active and pro-matrix metalloproteinase 9 (total MMP-9) and human vascular endothelial growth factor (VEGF) ELISA kits were obtained from R&D Systems, Inc. (Minneapolis, MN). Human plasminogen activator inhibitor-1 (PAI-1) and human tissue factor (TF) ELISA kits were obtained from American Diagnostica, Inc. (Greenwich, CT). All ELISAs were performed on plasma samples according to the manufacturers' instructions.

**2D gel analysis**

[0220] Patient plasma was analyzed by 2D gel electrophoresis by Kendrick Labs (Madison, WI) according to the method of O'Farrell (J. Biol. Chem. 250: 4007-4021, 1975). Briefly, 150 ug of plasma protein was separated by isoelectric focusing using pH 4-8 gradient IEF gels. A 10% SDS/PAGE gel was used for the second gel dimension. Limited computerized comparisons were carried out on duplicate silver-stained gels and the spot percentage was calculated according to the formula:  $\text{Difference} = (1 - \text{spot \% sample} \times \text{spot \% sample ref}) \times 100$ . Spots whose abundance appeared to differ after Compound A exposure were subsequently excised and MALDI-TOF analysis was carried out for identification purposes.

**Isolation of RNA from whole frozen blood**

[0221] TRI Reagent®BD – RNA, DNA, protein isolation reagent was used according to the manufacturer's protocol, Molecular Research Center, Inc. (Cincinnati, OH) <www.mrcgene.com>.

**Transcriptional Profiling Using Affymetrix DNA Arrays**

[0222] RNA processing and hybridization protocols were carried out as recommended by Affymetrix, Inc. (Santa Clara, CA); protocols are available in the Genechip® Expression Analysis Technical Manual <www.affymetrix.com/support/technical/manual/

expression\_manual.affx>. In brief, double-stranded cDNA was synthesized from total blood RNA (8 µg) of patient samples using Invitrogen Life Technologies SuperScript Choice system reagents (Carlsbad, CA). A T7-(dT)<sub>24</sub> oligomer was used to prime first-strand cDNA synthesis. Double-stranded cDNA product was generated and purified via phenol-chloroform extraction, then used as template for in vitro transcription (IVT) of cRNA. The IVT reaction was performed using BioArray High Yield RNA Transcript Labeling Kit (Affymetrix) according to manufacturer's protocol. The cRNA product was then purified with Qiagen RNeasy Mini Kit spin columns according to the manufacturer's protocol (Qiagen, Valencia, CA). Purified cRNA was quantitated, chemically fragmented, and hybridized overnight on Human Genome U95A Arrays. Hybridized arrays were washed and stained with phycoerythrin-conjugated streptavidin detection chemistry in an Affymetrix Fluidics station. Images were scanned with a Hewlett-Packard GeneArray scanner.

### **Data Analysis**

[0223] Data files were generated from scanned array images in the Affymetrix Microarray Suite Version 4.0 program. The two key parameters used in determining transcriptional changes are the Average Difference (AD) values, which serve as relative indicators of the expression level of transcripts represented on the arrays, and the Absolute Call (AC), which determines the presence or absence of each transcript. To enable comparison of all hybridization data, global scaling was applied by multiplying the output of each experiment by a scaling factor (SF) to make its average intensity equal to a user-defined Target Intensity (1000 for these experiments). For comparisons between time points from a single patient, the data were analyzed using Microsoft Access 97 software (Microsoft, Redmond, WA). To determine the fold change, the AD of the post-treatment sample was divided by the AD of the pre-dose samples. A data filtering step was carried out to identify transcripts with AC of "present" that showed a fold change  $\geq 1.7$  (increasing or decreasing).

### **TaqMan (qRT-PCR)**

[0224] Primers and probes were designed using Primer Express 2.0 software, and purchased from Applied Biosystems (Foster City, CA). In all cases, primers and probes were designed to hybridize to sequences represented by the Affymetrix probe set (see Affymetrix NetAffx website for detail). All probes contained a reporter dye (FAM) and a dye quencher (MGB). qRT-PCR was performed using 20 ng of total RNA with TaqMan® One-Step RT-



PCR Master Mix Reagents Kit (Applied Biosystems) following the manufacturer's protocol. The reactions were performed in 96-well optical plates and analyzed using the ABI PRISM® 7700 Sequence Detection System (Applied Biosystems). Thermal cycler conditions used are as follows: 48°C for 30 minutes, 95°C for 10 minutes, 95°C for 15 seconds followed by 60°C for 1 minute for 40 cycles, and 25°C for 2 minutes. VEGF (Genbank accession number AF022375) transcripts were amplified using forward primer GCTCTCTTATTTGTACCGGTTTTTG (SEQ ID NO: 165), reverse primer AAGCTAGTGACTGTCACCGATCAG (SEQ ID NO: 166), and probe TCATGTTTCCAATCTC (SEQ ID NO: 167) to generate an 82-bp amplicon product. Vinculin (Genbank accession number M33308) transcripts were amplified using forward primer CCTGATATAAATGCAATATTAATGCCTTTA (SEQ ID NO: 168), reverse primer AAGAACCGGGAGAGCAAACAT (SEQ ID NO: 169), and probe ATCTATGCCAAAGATCACTT (SEQ ID NO: 170) to generate a 124-bp amplicon product. PECAM-1 (Genbank accession number L34657) transcripts were amplified using forward primer GGAGCACCGCCTGTGAA (SEQ ID NO: 171), reverse primer TGTGCGTTGCCTGAATGAAC (SEQ ID NO: 172), and probe ACCAACCTGAAGACAC (SEQ ID NO: 173) to generate a 56-bp amplicon product. MAPK Kinase 3 (Genbank accession number L36719) transcripts were amplified using forward primer TCTCGACTGAATGGACTTTGCA (SEQ ID NO: 174), reverse primer TTGTGTACCCCGCACCAA (SEQ ID NO: 175), and probe CACACCTCTATCCCGGC (SEQ ID NO: 176) to generate a 77-bp amplicon product. Hemoglobin, epsilon 1 (Genbank accession number AI349593) transcripts were amplified using forward primer GCTGCATGTGGATCCTGAGA (SEQ ID NO: 177), reverse primer TGAGTAGCCAGAATAATCACCATCA (SEQ ID NO: 178), and probe CTTCAAGCTCCTGGGTAA (SEQ ID NO: 179) to generate a 66-bp amplicon product. GAPDH and 18S were ordered as pre-developed assay reagents (PDARs) from Applied Biosystems and used as endogenous controls.

**[0225]** Data analysis of TaqMan (qRT-PCR): The Ct scores represent the cycle number at which fluorescence signal ( $\Delta R_n$ ) crosses an arbitrary (user-defined) threshold. The Ct scores for genes of interest for each sample were normalized against Ct scores for the corresponding endogenous control gene (GAPDH or 18S). Relative expression of specific transcripts in the post-dose sample compared to pre-dose sample was determined by the

following calculation, as described in the Applied Biosystems users bulletin on Relative Quantitation of Gene Expression:

$$\text{Rel Exp} = 2^{-\Delta\Delta\text{Ct}},$$

$$\text{Where } \Delta\Delta\text{Ct} = (\text{Ct}_{\text{target}} - \text{Ct}_{\text{control}})_{\text{post-dose}} - (\text{Ct}_{\text{target}} - \text{Ct}_{\text{control}})_{\text{pre-dose}}.$$

## **2. Studies using Compound A – Results**

### **ELISAs**

[0226] Samples of plasma from human patients were taken before and 24 hours after the first dose of Compound A (SU6668). The patients were dosed twice over 24 hours with Compound A. The results of the ELISA analysis are shown in Figure 1, which shows that the levels of PAI-1, VEGF and TIMP-1 were increased in the plasma from patients exposed to Compound A. These proteins were therefore identified as biomarkers for a compound that inhibits tyrosine kinase, such as Compound A. These patients were suffering from various types of cancer.

### **Two Dimensional Polyacrylamide Gel Electrophoresis**

[0227] Samples of plasma from human patients suffering from advanced solid malignancies were taken before and 4 hours after the first (and only) dose of Compound A. A variety of proteins were increased and/or decreased in the plasma of patients treated with Compound A. As shown in Figures 2 and 3, mass spectrometry analysis identified one of these proteins (spot # 5) as ITIH4 (inter alpha (globulin) inhibitor H4). ITIH4 was therefore identified as a biomarker for a compound that inhibits tyrosine kinase, such as Compound A. See Figure 12 for sequences for ITIH4.

### **Microarrays and RT-PCR Analysis**

[0228] Samples of whole blood from human patients suffering from advanced solid malignancies were taken before and 24 hours after the first dose of Compound A. An Affymetrix GeneChip analysis of the RNA transcripts present in patient blood before and after exposure to Compound A indicated that the levels of vinculin and VEGF RNA increase after exposure to Compound A (see Figure 4A and 4B). Vinculin and VEGF were therefore identified as a biomarker for a compound that inhibits tyrosine kinase, such as Compound A.

**Microarrays and RT-PCR Analysis**

[0229] Samples of whole blood from human patients were taken before and 27 days after the first dose of Compound A (in other words, samples were taken on day 0 and day 28; patients were dosed about 2 times per day on day 1-day 27, and following the first dose on day 28, the sample of blood was taken to measure biomarker(s). An Affymetrix GeneChip analysis of the RNA transcripts present in patient plasma before and after exposure to Compound A indicated that the levels of 26 transcripts were increased and/or decreased after exposure to Compound A (see Figure 5). Thus, 26 proteins/transcripts were identified as biomarkers for a compound that inhibits tyrosine kinase, such as Compound A: eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06792), Homo sapiens thymosin beta-10, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. AI541256 (cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, human KIAA0195, Homo sapiens MAP kinase kinase 3 (MKK3), human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B member R, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA). See Figure 12 for sequences for these biomarkers.

**E. EXAMPLES – STUDIES USING COMPOUND B (SU5416)****1. Studies using Compound B – Materials and Methods****Study Population**

[0230] Patient samples were derived from 2 randomized, open-label, multicenter Phase III clinical trials comparing standard of care chemotherapy alone or combined with Compound B in patients with metastatic colorectal cancer. In both trials Compound B was delivered twice weekly at a dose of 145 mg/m<sup>2</sup> via I.V. infusion. In the first trial (designated Trial A), the standard of care chemotherapy consisted of weekly administration of 5-FU and leucovorin (Rosewell Park regimen); in the second trial (designated Trial B), the standard of care chemotherapy consisted of weekly or bi-weekly administration of 5-FU, leucovorin and

Irinotecan (CPT-11). A total of 23 patient sample pairs were included in Affymetrix microarray expression profiling analysis, 2 females and 9 males in the Compound B treatment arm, and 2 females and 10 males in the control arm. The median patient age was 66 and 65 years for the Compound B treatment arm and control arm, respectively. For RT-verification experiments, samples from 12 females and 24 males from the Compound B treatment arm, and 14 females and 17 males from the control arm were used. The median age for these patients was 62 and 60 years, respectively. Clinical response criteria were defined according to RECIST guidelines. Briefly, complete response (CR) is defined as complete disappearance of all measurable and evaluable clinical evidence of cancer; partial response (PR) is defined as at least a 50% reduction in the size of all measurable tumor areas; progressive disease (PD) is defined as an increase of  $\geq 25\%$  (compared to baseline or best response) in the size of all measurable tumor areas; and stable disease (SD) is defined as neither sufficient shrinkage to quantify for PR nor sufficient increase to qualify for PD.

#### **Patient samples**

[0231] All clinical samples for biomarker analysis were harvested and handled in accordance with full Institutional Review Board-approved protocol, and study participants had signed the study informed consent prior to any study related procedures. All blood samples were collected into Vacutainer tubes containing sodium heparin. Ten 10 ml of blood was withdrawn from patients prior to receiving any treatment on day 1 and also prior to dosing at end of cycle 1 (day 56 in Trial A; day 42 in Trial B). For peripheral blood mononuclear cell (PBMC) preparations, blood samples were shipped overnight at ambient temperature to a central processing facility (Quest Diagnostics, Inc., Collegeville, PA, USA) for PBMC isolation via Ficoll gradient method. Purified PBMCs were shipped in RNA lysis buffer (Clontech, Palo Alto, CA, USA) to SUGEN where isolation of total RNA was performed. For Trial B, whole peripheral blood samples were directly frozen at the clinical sites and shipped on dry ice to SUGEN for RNA isolation.

#### **RNA sample processing**

[0232] Total RNA was purified from PBMC samples using Clontech Nucleospin RNA II kit reagents (Clontech, Palo Alto, CA) and from whole blood samples using MRC

TRI Reagent BD (Molecular Research Center, Cincinnati, OH, USA), an adaptation of the Chomczynski single step method, according to the manufacturer's instructions. All sample preparations included a treatment with RNase-free DNase. RNA yields were measured by UV absorbance and RNA quality was assessed by agarose gel electrophoresis with ethidium bromide staining for visualization of ribosomal RNA band integrity.

### **Affymetrix high-density oligonucleotide microarray analysis of PBMC expression profiles**

[0233] In general, the standard RNA processing and hybridization protocols as recommended by Affymetrix (Santa Clara, CA, USA) were followed in this study; these protocols are available in the Genechip® Expression Analysis Technical Manual (viewable at <[www.affymetrix.com/support/technical/manual/expression\\_manual.affx](http://www.affymetrix.com/support/technical/manual/expression_manual.affx)>. Yields of total RNA for PBMC samples were generally low and for the majority of patients it was not possible to use the standard amount of total RNA ( $\geq 5 \mu\text{g}$ ) as recommended in the standard protocol. Therefore a double linear amplification approach was used in the generation of cRNA for hybridization. In these experiments, equal amounts of starting material were used for pre- and post-treatment samples from each donor (typically  $2 \mu\text{g}$ ). Briefly, the protocol was as follows: double-stranded cDNA was synthesized from total RNA ( $2 \mu\text{g}$ ), with Invitrogen Life Technologies SuperScript Choice system reagents (Invitrogen, Carlsbad, CA). The T7-(dT)<sub>24</sub> oligomer was used for priming first-strand cDNA synthesis. Double-stranded cDNA product was purified via phenol-chloroform extraction, then used as template in first round of in vitro transcription (IVT) of cRNA. The IVT reaction was performed with BioArray HighYield RNA Transcript Labeling Kit (Affymetrix) according to manufacturer's protocol but with substitution of non-biotinylated ribonucleotides for biotinylated ribonucleotides. The cRNA product was then purified with Qiagen spin column clean-up protocol and used as template in second round of cDNA synthesis. This second round of synthesis was similar to the first round except that random hexamers were used in priming of first-strand synthesis, with T7-(dT)<sub>24</sub> oligomer priming the second-strand. Purification of the cDNA was as in the first round. The second round of IVT of cRNA was as in the first round but with biotinylated ribonucleotides rather than non-biotinylated ribonucleotides. Purified cRNA was quantitated, chemically fragmented according to Affymetrix protocol, and then hybridized overnight on Human Genome U95A Arrays (which contain probe sets for the detection of approximately 12,600

transcripts). Hybridized arrays were washed and stained with phycoerythrin-conjugated streptavidin detection chemistry in an Affymetrix Fluidics station, then images were scanned with a Hewlett-Packard GeneArray scanner.

### **Data Analysis**

**[0234]** Data files were generated from scanned array images in the Affymetrix Microarray Suite Version 4.0 program. The key output from individual arrays are the Average Difference (AD) values, which serve as relative indicators of the expression level of transcripts represented on the arrays. Average Difference determination relies on difference between background-subtracted signal from perfect match (PM) oligos and corresponding mismatch control (MM) oligos within a probe set representing a given transcript. To enable comparison of all hybridization data, global scaling was applied by multiplying the output of each experiment by a Scaling factor (SF) to make its average intensity equal to a user-defined Target Intensity (which was set at 1500 for these experiments). For comparisons between time points from a single patient, batch files were generated with Microarray Suite. These files contain calculated fold change (FC) values, which represent differential expression ratios of day 56 compared to baseline, and also Difference Calls (DC), which represent a more conservative estimate of differential expression, with qualitative scores assigned to each transcript measurement according to the following system: Increased (I), Marginally Increased (MI), No Change (NC), Marginally Decreased (MD), and Decreased (D).

**[0235]** Subsequent data analysis was performed primarily with Spotfire DecisionSite for Functional Genomics software (version 7) package and its Array Explorer component (Spotfire, Somerville, MA). Hierarchical clustering analysis and statistical comparisons were included in this step. Further refinement of the data, including filtering by Difference Call scores, was done with the Microsoft Access 97 database analysis program.

### **SYBR Green quantitative RT-PCR verification of array results**

**[0236]** Primers were designed with Primer Express 1.5 software (Applied Biosystems). In all cases, primers were designed to bind within the sequence that was used in Affymetrix probe set designs (target sequence information available on Affymetrix NetAffx website). Total RNA samples (1 µg) were reverse transcribed to yield first-strand cDNA using the Applied Biosystems Reverse Transcription Reagents protocol (Applied Biosystems, Foster City, CA). The reverse transcription reactions were then diluted 1:5 in distilled H<sub>2</sub>O.

SYBR Green PCR reactions were performed in 96-well optical plates and run in an ABI PRISM® 7700 Sequence Detection System (SDS) machine. For individual reactions, 10 µl of each sample were combined with 15 µl of SYBR Green PCR Master Mix (Applied Biosystems) containing the appropriate primer pair at 350 nM. Data was extracted and amplification plots generated with ABI SDS software. All amplifications were done in duplicate and threshold cycle ( $C_t$ ) scores were averaged for subsequent calculations of relative expression values. The  $C_t$  scores represent the cycle number at which fluorescence signal ( $\Delta R_n$ ) crosses an arbitrary (user-defined) threshold. Heat dissociation curve analysis was performed after each SYBR Green run as a test of whether a single product had been generated in each PCR reaction; multiple peaks in the dissociation curves are indicative of multiple PCR products and thus reduced specificity and sensitivity.

#### **Quantitation and statistical analysis of SYBR Green PCR data**

[0237] The  $C_t$  scores for genes of interest for each sample were normalized against  $C_t$  scores for the corresponding endogenous control gene, which was the  $\beta$ -glucuronidase (GUS) gene in these experiments. Relative expression for day 56 compared to day 1 was determined by the following calculation, as described in the Applied Biosystems users bulletin on Relative Quantitation of Gene Expression:

$$\text{Rel Exp} = 2^{-\Delta\Delta C_t},$$

Where  $\Delta\Delta C_t = (C_{t \text{ Target}} - C_{t \text{ GUS}})_{\text{day 56}} - (C_{t \text{ Target}} - C_{t \text{ GUS}})_{\text{day 1}}$ .

[0238] The relative expression data for a select subset of potential biomarkers were tested for differences between the Compound B (treatment) and the standard of care (control) arms. The Mann-Whitney U Test with a critical alpha level of 0.05 was used for statistical significance. Individual genes observed to be significantly different by Affymetrix analysis and in both sets of SYBR Green RT-PCR experiments were screened as potential biomarker candidates. This subset of potential biomarker candidates was tested subsequently for utility as class predictors to discriminate between the Compound B and standard of care arms. Discriminant analysis, a multivariate statistical technique, was used for this purpose. The genes were tested individually, using all possible combinations, by reducing dimensions (Principal Component Analysis) in order to determine the subset of genes (predictor variables) that yielded highest classification accuracy. Cross-validation was used to test the robustness of classification accuracy. Results from three different cross-validations were evaluated to select the best set of predictable biomarkers: (1) jackknife method (dropping

one case at a time); (2) randomly splitting the pooled data into two halves, prediction (for building model) and validation (for testing model); and (3) using the first trial as prediction and the later trial as validation sets, respectively. All statistical analyses were carried out after natural-log transformation on the data; SYSTAT 9.01 (SPSS, Inc., Chicago, IL, USA) software was used in statistical analysis.

## **2. Studies using Compound B – Results**

### **Affymetrix expression profiling of pre- and post-treatment matched PBMC samples**

**[0239]** Expression profiling using Affymetrix high-density oligonucleotide microarrays was applied to PBMC samples harvested from patients in a Phase III clinical trial of Compound B in Trial A. The PBMC samples were harvested at baseline (day 1) and at end of cycle 1 (day 56) from patients receiving standard-of-care (5-FU/leucovorin) treatment and from those receiving standard-of-care plus Compound B. Sample pairs from 23 patients were processed and the dataset was filtered for expression changes that consistently correlated with the treatment arm (Compound B). Of 13 genes that met the initial requirement, 6 were further tested by quantitative RT-PCR analysis of additional patient samples from patients.

**[0240]** Table 1 includes a summary of the total samples processed. As RNA yields rarely exceeded 2 µg, a double amplification step was used in cRNA generation for the samples that were used (see Materials and Methods). Only samples from patients with cycle 1 responses of either PR/CR or PD were used in the final dataset.

**[0241]** Batch comparison files were generated for each day 1/day 56 sample pair after hybridization. Batch comparisons included both fold change (FC) values as calculated by Affymetrix Microarray Suite software as well as difference calls (DC). DC offer a more stringent but non-numerical measure of whether levels of a transcript are different in the 2 samples. Batch comparison results for the 23 cases were analyzed with Spotfire Decision Site software tools. Initial analysis suggested there was more similarity among patient samples of the same treatment arm than among samples of the same response category (PR/CR or PD) independent of treatment arm. Therefore, subsequent analysis focused on identification of transcripts that were differentially expressed in the Compound B arm but not in the control arm.



[0242] The Treatment Comparison tool in Spotfire was used to identify transcripts that were statistically significantly different in the two treatment arms; this tool uses t-test analysis of averaged fold changes for each group. To further refine this subset of genes, queries based on DC status were performed with Microsoft Access. The data were filtered to identify those genes that were called 'Increased' (I) or 'Decreased' (D) in a majority of the Compound B arm cases. A group of 13 genes that frequently showed increased expression was identified. Figure 6 displays a schema of the DC scores assigned to each gene for each patient sample pair. All cases from the Compound B arm show induction in at least 6 of the 13 genes.

[0243] Table 2 includes a brief summary of putative biological function for each of the 13 gene products, as well as an ID number assigned by Affymetrix to each transcript-specific probe. The last two columns in Table 2 list the number of patients in which transcript levels were increased at day 56 relative to day 1 (i.e., an 'Increase' call was assigned). Total number of patients is 11 for the Compound B (SU5416) arm and 12 for the control arm. The average fold change of all of these transcripts was higher in the Compound B (SU5416) arm (the lowest average fold change was 2.6 for hypothetical protein FLJ13052, the highest was 33 for lactoferrin); the range of fold changes was also broader in this category, presumably representing variability among patients.

### **Quantitative RT-PCR validation of differentially expressed transcripts**

[0244] To validate the microarray results, a subset of these transcripts was chosen for quantitative RT-PCR analysis. Primer sets were designed for 6 of the 13 genes; matrix metalloproteinase-9 (MMP-9), thrombospondin-1 (TSP-1), CD24, defensin  $\alpha$  3, lipocalin 2 (LCN2), and lactoferrin. These 6 genes were chosen based on potential roles of encoded proteins (for example, thrombospondin-1 and MMP-9 have known roles in angiogenesis) or because of the degree to which they appeared to be differentially regulated between treatment arms. The lipocalin-2 gene (LCN2) has been reported to be inducible by dexamethasone (Science, 293: 829-34 (2001)). Dexamethasone is one of the premedications administered to patients in the Compound B arm. Table 3 describes the forward and reverse primers that were used in validation of these transcripts.

[0245] SYBR Green chemistry was used to validate the microarray expression profiling data. SYBR Green is a dye that fluoresces when bound to double-stranded DNA,

thus signal is directly proportional to the amount of product formed during PCR amplification. This method allows rapid and inexpensive comparison of gene expression across a large number of samples. The qRT-PCR validation was performed with a total of 31 Compound B patient sample pairs, 8 of which had previously been analyzed on Affymetrix U95A arrays and thus allowed a comparison of the correlation between the 2 transcript profiling methods. Of the 31 samples, 18 were from the Compound B arm and 13 were from the control arm.

[0246] Data for each gene was normalized to expression of a housekeeping gene,  $\beta$ -glucuronidase (GUS). By direct comparison of SYBR Green RT-PCR results and Affymetrix results from the same cases, the overall qualitative correlation (i.e., same trend of induction or no change detected in both samples) was greater than 70%. This number is perhaps an underestimate since results for one patient were completely discordant between methods and thus potentially due to experimental artifact.

[0247] Figure 7 summarizes the results from the RT-PCR validation and compares them with those from the Affymetrix analysis. It is clear that there are some differences in the trends displayed in the 2 datasets. This is further demonstrated by statistical analysis, as Mann-Whitney U test comparison of Compound B and control results from both analyses indicates that only 4 of the 6 genes display statistical significance (Table 4). These 4 genes are CD24, lactoferrin, LCN2, and MMP-9. (MMP-9 exhibited a p-value that was close to the significance cutoff and thus was also selected for further analysis.)

#### **Qualitative RT-PCR validation of differentially expressed transcripts with samples from a second Phase III Compound B trial**

[0248] To further confirm these transcripts as biomarkers of Compound B administration, SYBR Green RT-PCR analysis of these 4 transcripts was carried out in a collection of samples from a second Phase III trial (Trial B). In this randomized metastatic colorectal cancer study, 5-FU/leucovorin/CPT-11 was administered as the standard of care, and compared to the standard of care plus Compound B. RNA samples from patients in this trial were derived from frozen whole blood (rather than purified PBMCs), and harvested at the beginning (pre-dose day 1) and at the end (day 42) of cycle 1. To test if similar results occurred, analysis was performed on 36 sample pairs, 18 from Compound B arm and 18 from control arm. Due to limited numbers of available samples, many of the cases analyzed in this

analysis were from patients with stable disease (SD) at cycle 1 assessment rather than PR/CR and PD as in the previous approaches.

[0249] Figure 8 summarizes the overall behavior of the transcript levels in both trial arms in terms of the frequency with which the transcripts showed an induction (here defined as relative expression, day 42 vs day 1) of 2-fold or greater in each arm. It is clear that there is more induction of these transcripts at day 42 in the Compound B arm than in the control arm. This is also reflected in statistical analysis, as indicated in results of the Mann-Whitney U Test of this dataset (Table 5).

[0250] A visual representation of hierarchical clustering analysis of the qRT-PCR relative expression values from both trials for each of the transcripts is displayed in Figure 9. This clustering pattern displays the distinction between the Compound B and control arms based on relative expression data, and also indicates further distinctions among subsets of patients as well as the degree of overlap between trial arms in the clustering pattern. The extent of similarity between the relative expression patterns for each transcript (represented in columns) is also indicated; the pattern of MMP-9 is distinct from the others as it appears in a separate branch in the dendrogram structure.

#### **Discriminant analysis of the classification power of biomarkers**

[0251] We tested whether relative expression data from these samples could be used in a predictive fashion to classify samples to the appropriate trial arm. To test this, discriminant analysis of the SYBR Green RT-PCR data was performed. Relative expression values from both the first and the second dataset were combined, after comparison of mean relative expression ratios and standard deviations indicated greater similarity between respective trial arms rather than between control and Compound B arm in either trial alone. The relative expression ratios were then natural log-transformed to reduce the scale of the values and thus make control and treated arms more comparable. When the samples were pooled (67 cases altogether) and subjected to classification prediction, a total prediction accuracy of 84% was achieved. Further cross-validation was performed by the jack-knife method (which does a series of predictions, randomly removing 1 case from the total each time), and by splitting the data set into 2 random halves (one a 'training' set and the other a 'testing' set).

**[0252]** The results from each of these steps are summarized in Table 6 for a set of 3 of the 4 transcripts that gave the best accuracy percentage (including MMP-9 slightly reduced the accuracy of cross-validation). Thus, it is predicted that expression data from these 3 genes would accurately distinguish Compound B arm patients from control arm in between 67% to 84% of cases. When the first trial data was used as the 'training' set and the second trial data as the 'testing', as opposed to randomly selecting the data, the % accuracy in cross-validation was 86% and 77% for the training and testing set, respectively. Cross-validation results are displayed for two different approaches. In section 2 of Table 6, one case is dropped at a time and its group membership predicted from the other cases. In sections 3 and 4, cross-validation is carried out by using a randomly selected half of the cases as a training set and the remaining half as a test set. Section 4 summarizes the prediction accuracy achieved when the group in section 3 is used as a training set.

#### **Conclusions: Compound B Studies**

**[0253]** Large-scale gene expression analysis was applied to blood RNA samples from a clinical trial of Compound B to investigate changes in gene expression that might correlate with exposure to cancer therapy. Independent quantitative RT-PCR validation of initial array hybridization results was performed on larger sample populations from two conceptually similar Phase III clinical trials using Compound B. A set of 4 transcripts (CD24, lactoferrin, LCN2, and MMP-9) was identified whose expression was significantly induced at the end of one treatment cycle relative to baseline following Compound B administration. Discriminant analysis indicates that data derived from the RT-PCR study would have a class prediction accuracy of at least 70%.

**[0254]** These 4 transcripts are considered to be biomarkers of Compound B administration and other compounds that inhibit tyrosine kinase. These results also demonstrate that human blood samples can serve as surrogate tissues for biomarker investigations and that large-scale gene expression analysis is a useful approach for characterization of clinical trial samples.

**F. EXAMPLES – FURTHER STUDIES USING COMPOUND B (SU5416)****Baseline and post-treatment levels of PAI-1 in Compound B patient plasma**

[0255] PAI-1 plasma levels were examined in samples from Compound B patients. Interestingly, median PAI-1 levels decreased after 56 days of treatment in samples from all patients examined with a MR (minor response) at the end of cycle 1 (Figure 10, n = 37; Compound B arm day 1 median 40.66 ng/ml, day 56 median 23.93 ng/ml, 5FU/LV arm day 1 median 40.91 ng/ml, day 56 median 18.94 ng/ml). In contrast, median PAI-1 levels in samples from all patients examined with a PD (progressive disease) response at the end of cycle 1 did not appear to change significantly (Figure 10, n = 47; Compound B arm day 1 median 26.47 ng/ml, day 56 median 34.8 ng/ml, 5FU/LV arm day 1 median 25.67 ng/ml, day 56 median 23.29 ng/ml). Furthermore, the decrease in PAI-1 plasma levels in the control arm MR patients after 56 days of treatment was statistically significant (day 1 median 40.91 ng/ml, day 56 median 18.94 ng/ml,  $P = 0.0003$ ; n = 20). The decrease in PAI-1 levels of Compound B arm patients was not statistically significant ( $P = 0.095$ ; n = 17). These data indicate that changes in plasma PAI-1 levels after one cycle of treatment correlate with cycle one clinical response of both the experimental and control arm regimens.

**Pre-treatment levels of PAI-1**

[0256] An analysis of the pre-treatment plasma levels of plasminogen activator inhibitor-1 (PAI-1) shows that pre-treatment levels also correlate with clinical response (on day 56) in either arm, indicating that PAI-1 is a biomarker predictive of response to tyrosine kinase inhibitor in advanced colorectal cancer.

[0257] An analysis of the pre-treatment levels of PAI-1 indicated that patients with an MR response (cycle 1) had a statistically significantly ( $P = 0.001$ ) higher level of plasma PAI-1 (median 41 ng/ml; n = 37) than that of patients with a PD response (median 26 ng/ml; n = 47) regardless of the regimen subsequently received. Thus far, only 4 patients that had a partial response (PR) at the end of cycle 1 have been examined for PAI-1 plasma levels. These patients have pre-treatment levels (median 37.4 ng/ml) similar to the MR patients (median 40 ng/ml), however PAI-1 levels did not decrease significantly in these patients samples after 56 days of treatment. These results (see Figure 10) indicate that the pre-treatment levels of plasma PAI-1 are predictive of MR response (as compared to a PD response) to either the experimental or the control arm regimen.

[0258] The present invention includes a method for predicting the probability of whether a patient will respond positively to administration of a tyrosine kinase inhibitor, comprising measuring the level of PAI-1 in patient plasma, wherein a level of greater than 30 nanograms/per ml of plasma, or greater than at least 35 nanograms, or greater than at least 37 nanograms per ml, indicates a positive probability that the patient will respond positively to administration of a tyrosine kinase inhibitor.

## **G. EXAMPLES – STUDIES USING COMPOUND 1**

### **1. Studies using Compound 1 – Materials and Methods**

[0259] A panel of proteins were investigated for their utility as biomarkers of Compound 1 in cancer patients receiving the compound in Phase I trials. The patient samples were from a total of four Phase I trials, 3 of which were open to patients with any advanced solid malignancy (these were Trials A, B and C) and one of which (Trial D) was a trial in patients with Gleevec-refractory, resistant, or intolerant gastrointestinal stromal tumors (GIST). In all cases, plasma samples were available from just before first Compound 1, or malate salt thereof, dose (baseline) and at various time points during dosing. In Trials A and B, patients received Compound 1. In Trials C and D, patients received a malate salt of Compound 1. For methods of making Compound 1, *see* U.S. Ser. No. 09/783,264 or WO 01/60814, U.S. Ser. No. 10/076,140 or U.S. Ser. No. 10/281,985, the disclosures of which are incorporated by reference. For methods of formulating Compound 1, *see* U.S. Ser. No. 10/237,966 (now a U.S. provisional application), the disclosure of which is incorporated by reference.

[0260] All of the ELISA-based screening of candidate proteins were performed with commercially available ELISA kits; the kits for the biomarkers described in this report are all available from R&D Systems (Minneapolis, MN). A commercially available membrane array containing antibodies for the detection of 42 human cytokines was also used in screening of a patient's plasma samples before and after treatment. The antibody array used in cytokine screening (RayBio Human Cytokine Array III) was from RayBiotech (Norcross, GA).

[0261] All clinical plasma samples were harvested and handled in accordance with full Institutional Review Board-approved protocol. Study participants signed the appropriate informed consent prior to any study related procedures. Plasma was separated from blood

samples collected into Vacutainer tubes containing sodium heparin and shipped frozen to the SUGEN site. The time points for which plasma samples are available in each trial are as follows:

Trial A (4 weeks on/ 2 weeks off dosing schedule):  
plasma – Day 1 (0, 6, 24 hr); Day 28 (0, 6, 24 hr)

Trial B (2 weeks on/ 2 weeks off):  
Plasma – Day 1 (0, 6, 12, 24 hr); Day 13 (0, 6, 12, 24 hr)

Trial C (4 weeks on/ 2 weeks off):  
Plasma – Day 1 (0, 6 hr); Day 15, 29, 42\* (Cycle 1); Day 1, 15, 29 (Cycle 2)

Trial D (2 weeks on/ 2 weeks off):  
Plasma – Day 1, 7, 14, 28\* (Cycle 1); Day 1 only, in subsequent cycles

Trial E (4 weeks on/2 weeks off):  
Plasma – Day 1, 3, 28 (Cycle 1)

\* ‘washout’ sample

Plasma samples were also collected from a set of 10 SUGEN healthy donors; plasma was collected at 3 time points for each donor (day 1, 14, and 28) to mimic time points used in the Phase I trials and thus serve as controls for the normal level of fluctuation of plasma markers in the absence of Compound 1 treatment.

[0262] Data analysis was performed for each marker. This was done by generating ratios of plasma levels at various time points during treatment versus the plasma levels at baseline (pre-dose on day 1, cycle 1), or by comparing absolute plasma concentrations at times during treatment to the baseline absolute plasma concentrations. For correlative analysis, scatter plots were drawn and linear regressions were calculated comparing fold change (end of cycle 1 dosing to baseline) of each marker to corresponding values assigned to clinical parameters such as pharmacokinetics, drug dosage, and <sup>18</sup>FDG-PET functional imaging.

## **2. Studies using Compound 1 – Results**

[0263] A panel of candidate proteins was evaluated by ELISA analysis in plasma samples from cancer patients receiving Compound 1 or malate salt thereof. Of those investigated, a subset was observed to change consistently in patients receiving Compound 1 or malate salt thereof. One of the proteins was Vascular Endothelial Growth Factor (VEGF);

large increases (greater than 3-fold) in plasma levels were seen in approximately 70% of patients in Trials A, B and C, and in a small proportion of patients in Trial D.

**[0264]** Figure 13 displays typical pattern of VEGF plasma levels seen in Trial C. VEGF levels are observed to rise by day 15 of cycle 1 and typically peak at day 29, then tend to subside to near baseline levels by day 42, which is the end of the 2-week drug rest period, or 'washout', in these patients.

**[0265]** To further investigate this, levels of a related angiogenic factor, Placenta Growth Factor (PLGF), were measured in some of the same patients as in the VEGF tests. As shown in Table 7, levels of PLGF are induced in a majority of patient samples that were tested, and follow a similar pattern as VEGF in that levels are most induced at day 29 and decline by day 42.

**[0266]** A further question regarding VEGF and PLGF was whether the presence of VEGF/PLGF heterodimers in patients' plasma could be detected, and whether levels of the heterodimer could be modulated by treatment with Compound 1 or malate salt thereof. Heterodimers of VEGF and PLGF have been reported in the scientific literature. To measure heterodimers, a hybrid ELISA assay was used, combining reagents from both the R&D Systems VEGF and PLGF ELISA kits (where VEGF antibodies are used in capture step and PLGF antibodies are used in detection step).

**[0267]** The results of applying this assay to plasma samples from 3 patients are shown in Figure 14. Data from the same samples for VEGF and PLGF are also shown in the graphs in Figure 14. A similar pattern of induction of the VEGF/PLGF heterodimer as was seen for VEGF and PLGF was observed. In 3 of 3 patients tested, an increase in plasma levels of VEGF/PLGF heterodimer is observed, indicating that both PLGF and the VEGF/PLGF heterodimer are novel biomarkers of Compound 1 activity in patients.

**[0268]** Another protein, VEGF receptor 2 (VEGFR2) was investigated. VEGFR2 is one of the targets of Compound 1 and is important in angiogenesis. Whether soluble VEGFR2 is detectable via ELISA in plasma samples from cancer patients was investigated, as well as whether levels of the protein would change in response to treatment with Compound 1 or malate salt thereof.

**[0269]** Intriguingly, levels of the plasma soluble form of VEGFR2 were observed to decrease in the vast majority of patients (greater than 90%) in Trials A, B and C at chronic time points (13 days or more) after the start of treatment with Compound 1 or malate salt



thereof. Also, in Trial D, a dose-dependency of the sVEGFR2 decrease was seen, as changes were clearly observed in a cohort of patients in that trial receiving 50 mg daily doses of a malate salt of Compound 1, but not observed in a cohort of patients receiving 25 mg daily doses (Figure 15). The difference between the dose cohorts was statistically significant as judged by t-test. Also, levels of sVEGFR2 typically increased to near baseline levels at the end of the 2-week drug rest period in patients from all 4 trials, thus exhibiting a pattern similar in timing but opposite in direction to that seen for VEGF and PLGF (Table 9). Table 9 displays results for sVEGFR2 in individual patients, and also includes results for PLGF where available. Also included in Table 9 is information on the types of cancers found in the patients.

[0270] Further, data suggests that there exists some correlation between the extent of decrease in plasma sVEGFR2 and pharmacokinetics measurements of drug exposure in patients. This is demonstrated in Figure 16, which shows a scatter graph plotting change in sVEGFR2 plasma level (ratio of level on last day of cycle 1 dosing to baseline level) against area under curve (AUC) drug exposure measurements (from last day of cycle 1 dosing). The graph is a composite of data from all 4 trials, and the R-squared value indicates there is some association between decrease in sVEGFR2 and drug exposure. Thus, soluble VEGFR2 is a novel marker of Compound 1 treatment and may be a marker of both drug exposure and biological activity of the compound.

[0271] Another potential biomarker of Compound 1 was identified first in an array-based screen of plasma samples, before and after Compound 1 treatment, from a patient in Trial B. The array screen utilized a commercially available antibody membrane array, which in principle allows for simultaneous measurement of 42 different human cytokines. Results of the screen indicated that levels of a protein called Monokine Induced by Interferon-gamma, or MIG, were significantly higher after treatment with Compound 1 than in baseline samples. This result was confirmed via an MIG ELISA assay on the same patient samples. Following confirmation, levels of MIG in plasma were assessed for a number of patients from Trial C. These results showed that MIG was induced more than 3-fold in 30-40% of the patients tested (data not shown).

[0272] There is evidence of a correlation between increased MIG levels and a positive response in the functional imaging assay of  $^{18}\text{F}$ FDG-PET (a feature of Trials C and D). This is illustrated in Figure 17; those patients with at least a mixed response based on PET imaging tended to have higher folds of induction of secreted MIG protein. To further

investigate the induction of MIG observed in patients, we have also measured the plasma levels of IP-10 and I-TAC before and after treatment with Compound 1 or malate salt thereof. IP-10 and I-TAC, like MIG, are regulated at the expression level by interferon-gamma, and both IP-10 and MIG have roles in chemoattraction of immune cells and exhibit angiostatic (anti-angiogenic) activity. Interestingly, evidence suggests that MIG and IP-10 are induced in tandem in 6 of 6 patients checked for both proteins while MIG and I-TAC are induced in tandem in 5 of 5 (Table 8). Similarly, all 3 proteins are induced in the 2 patients where all of the 3 were checked (Table 8). Table 10 indicates the types of cancer found in patients where MIG is induced. Thus, evidence indicates that MIG, IP-10 and I-TAC are novel biomarkers that are modulated in Compound 1 patients and are markers that correlate with an anti-tumor response as measured by PET imaging.

**[0273]** In summary, ELISA-based screening of plasma samples from Phase I clinical trials using Compound 1, or malate salt thereof, has yielded a set of circulating proteins that are novel surrogate markers for Compound 1 drug exposure and/or biological activity. Soluble VEGFR2 has been identified in plasma as a marker of drug exposure, while VEGF, PLGF, and VEGF/PLGF heterodimers have been frequently observed to increase in a majority of patients and appear to be correlates of biological activity and (to a lesser extent than sVEGFR2) drug exposure. MIG, IP-10 and I-TAC are additional biomarkers that appear to correlate with anti-tumor activity as measured by <sup>18</sup>FDG-PET functional imaging.

## H. EXAMPLES – FURTHER STUDIES USING COMPOUND 1

### 1. Further studies using Compound 1 – Materials and Methods

#### *In Vivo* Animal Studies

[0274] Female athymic-*nu/nu* mice (Charles River, Hollister, CA) were injected with Colo205 human colon cells ( $5 \times 10^6$  cells) subcutaneously. The animals were treated with a single dose of either citrate vehicle or Compound 1 at 40 mg/kg when the tumors are approximately 350-400 mm<sup>3</sup> in size. For biomarker studies, tumors were harvested at six and 24 hours post-treatment and snap frozen for RNA extraction.

#### Transcriptional Profiling Using Affymetrix DNA Arrays

[0275] RNA processing and hybridization protocols were carried out as recommended by Affymetrix, Inc. (Santa Clara, CA); protocols are available in the Genechip® Expression Analysis Technical Manual <[www.affymetrix.com/support/technical/manual/expression\\_manual.affx](http://www.affymetrix.com/support/technical/manual/expression_manual.affx)>. In brief, total RNA from tumor samples was prepared using Nucleospin RNA II Kit in accordance with the manufacturer's recommendation (Clontech, Palo Alto, CA). RNA processing and hybridization protocols were carried out as recommended by Affymetrix, Inc. (Santa Clara, CA); protocols are available in the Genechip® Expression Analysis Technical Manual <[www.affymetrix.com/support/technical/manual/expression\\_manual.affx](http://www.affymetrix.com/support/technical/manual/expression_manual.affx)>. In brief, double-stranded cDNA was synthesized from total RNA (8 µg) of tumor samples using Invitrogen Life Technologies SuperScript Choice system reagents (Carlsbad, CA). A T7-(dT)<sub>24</sub> oligomer was used to prime first-strand cDNA synthesis. Double-stranded cDNA product was generated and purified via phenol-chloroform extraction, then used as template for *in vitro* transcription (IVT) of cRNA. The IVT reaction was performed using BioArray HighYield RNA Transcript Labeling Kit (Affymetrix) according to manufacturer's protocol. The cRNA product was then purified with Qiagen RNeasy Mini Kit spin columns according to the manufacturer's protocol (Qiagen, Valencia, CA). Purified cRNA was quantitated, chemically fragmented, and hybridized overnight on Human Genome U95A Arrays. Hybridized arrays were washed and stained with phycoerythrin-conjugated streptavidin detection chemistry in an Affymetrix Fluidics station.

Images were scanned with a Hewlett-Packard GeneArray scanner. All techniques were performed on xenograft tissue samples according to the manufacturers' instructions.

#### **Data analysis of DNA microarray**

[0276] Data files were generated from scanned array images in the Affymetrix Microarray Suite Version 4.0 program. The two key parameters used in determining transcriptional changes are the Average Difference (AD) values, which serve as relative indicators of the expression level of transcripts represented on the arrays, and the Absolute Call (AC), which determines the presence or absence of each transcript. To enable comparison of all hybridization data, global scaling was applied by multiplying the output of each experiment by a scaling factor (SF) to make its average intensity equal to a user-defined Target Intensity (1500 for these experiments). For comparisons between different treatments from a single time point, the data were analyzed using Microsoft Access 97 software (Microsoft, Redmond, WA). To determine the fold change, the AD of the drug-treated samples was divided by the AD of the vehicle-treated samples. A data filtering step was carried out to identify transcripts with AC of "present" that showed a fold change  $\geq 2.0$  (increasing or decreasing).

#### **Taqman Real-Time RT-PCR Assay**

[0277] Primers and probes were designed using Primer Express 2.0 software (Applied Biosystems, Foster City, CA). All primers and probes were designed to hybridize to sequences represented by the Affymetrix probe set (see Affymetrix NetAffx website for detail). Taqman probes were labeled with reporter dye, 6-carboxy-fluorescein phosphoamidite (FAM), at the 5' end and dye quencher, minor groove binder (MGB), at the 3' end. Each 25- $\mu$ l reaction consisted of 500 nm forward primer, 500 nm reverse primer, 100 nm of Taqman probe, cDNA (20 ng of total RNA from tumor samples), and 1X (final concentration) of Taqman® One-Step RT-PCR Master Mix Reagents Kit (Applied Biosystems). The reactions were performed in 96-well optical plates and analyzed using the ABI PRISM® 7700 Sequence Detection System (Applied Biosystems). Thermal cycler conditions used are as follows: 48°C for 30 minutes, 95°C for 10 minutes, 95°C for 15 seconds followed by 60°C for 1 minute for 40 cycles, and 25°C for 2 minutes. 18S ribosomal gene's primers and probe pairs were purchased from Applied Biosystems and used according

to manufacturer's recommendation as an endogenous control. All techniques were performed on the tissue samples according to the manufacturers' instructions.

#### **Data analysis of Taqman assay**

[0278] The Ct scores represent the cycle number at which fluorescence signal ( $\Delta R_n$ ) crosses an arbitrary (user-defined) threshold. The Ct score for genes of interest for each sample were normalized against Ct score for the corresponding endogenous control gene (18S). Relative expression of specific transcripts in the drug-treated sample compared to vehicle-treated sample was determined by the following calculation, as described in the Applied Biosystems users bulletin on Relative Quantitation of Gene Expression:

$$\text{Relative Expression} = 2^{-\Delta\Delta C_t},$$

where  $\Delta\Delta C_t = (C_{t \text{ target}} - C_{t \text{ 18s control}})_{\text{drug treatment}} - (C_{t \text{ target}} - C_{t \text{ 18s control}})_{\text{vehicle treatment}}$ .

## **2. Further Studies using Compound 1 – Results**

### **Microarrays and RT-PCR Analysis**

[0279] To identify biomarker(s), samples of tissue from the tumors were taken before and after the first dose of Compound 1. An Affymetrix GeneChip analysis of the RNA transcripts present in xenograft tissue before and after exposure to Compound 1 indicated that the levels of 28 transcripts increased and/or decreased after exposure to Compound 1 (see Table 11A and 11B). Thus, the following 26 proteins/transcripts were identified as biomarkers for a compound that inhibits tyrosine kinase, such as Compound 1: basic transcription factor 3 homologue, human c-jun proto-oncogene, human c-fos proto-oncogen, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, vinculin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, gelsolin and cyclin D2. See Figure 24 for sequences for these biomarkers.

[0280] To validate the Affymetrix GeneChip results, a subset of 11 of these 26 transcripts was chosen for quantitative RT-PCR analysis. These 11 transcripts were chosen

based on potential roles of encoded proteins. Table 13 describes the forward and reverse primers that that were designed and used in the RT-PCR experiments. The results of the quantitative RT-PCR analysis for these 11 transcripts are shown in Table 12. The RT-PCR analysis confirms the findings with the Affymetrix GeneChip analysis for these 11 transcripts.

**I. EXAMPLES – ADDITIONAL STUDIES USING COMPOUND 1****1. Additional studies using Compound 1 – Materials and Methods****Human Umbilical Vein Endothelial Cells (HUVECs)**

[0281] HUVECs were obtained from Clonetics (San Diego, CA catalog# CC-2517) and were maintained in EGM media (Clonetics, catalog# CC-3121) containing EGM BulletKit (Clonetics, catalog# CC-4133: 2% Fetal Bovine Serum, 0.1% Epidermal Growth Factor, 0.1% Hydrocortisone, 0.1% Gentamicin Sulfate Amphotericin B, 0.4% Bovine Brain Extract). Cells were propagated at 37°C in a humidified atmosphere of 5% CO<sub>2</sub> using standard cell culture techniques. Cells were plated in 10-cm tissue culture plates at 8.5 X 10<sup>5</sup> cells/ml. After 6 hours the cells were quiesced by serum starvation overnight in starvation medium (EBM containing 0.5% FBS). DMSO (Sigma Chemicals, St. Louis, MO #D2650) or Compound 1 (to a final concentration of 10 nM, 100 nM, and 1 µM) were added to cells. After 2 hours of exposure to Compound 1 or DMSO, VEGF<sub>165</sub> (R&D Systems, Minneapolis, MN; catalog# 293VE050) was added to a final concentration of 100 ng/ml; no VEGF was added to samples that are subsequently referred to as the “baseline” samples. After a 10-min, 8 hr, 24 hr and 48h VEGF stimulation the conditioned medium was filtered through 0.45 µM syringe filter from Pall Gelman Laboratory (Ann Arbor, MI catalog# 4560) and immediately frozen on dry ice. Conditioned media was stored at -70°C until subsequent analysis.

**Analysis of Conditioned Media by 2D gel electrophoresis**

[0282] Thawed conditioned media samples were precipitated with three volumes of acetone for 2 hours at -20°C, then centrifuged at 13000 RPM for 15 minutes. Pellets were washed with the 2D Clean-Up Kit (Amersham, Cat. # 80-6484-51) as per protocol, air dried for three minutes, then resuspended in 8M urea (Amersham), 100 mM dithiothreitol (Fisher), 4% CHAPS (3[(cholamidopropyl)dimethylammonio]propanesulfonate from Calbiochem), and placed in a thermomixer (Eppendorf) at 600 RPM and 25°C for 2 hours. Protein was quantitated with Bio-Rad Protein Assay (cat# 500-0006) using the microassay for cuvettes protocol.

[0283] Samples were diluted to 0.3 µg/µl with IEF Buffer containing 1% IPG Buffer pH 3-10 (Amersham). Eighteen centimeter IPG strips pH 3-10 (Amersham) were rehydrated with 120 µg sample (400 µL) under Drystrip Cover Fluid (Amersham) on the IPGphor (Amersham) at 20°C for 18 hours. Strips were focused with the following program:

200 volts for 1 hour, ramped from 200 volts to 1000 volts over two hours, held at 1000 volts for 1 hour, ramped from 1000 volts to 8000 volts over 6 hours, then held at 8000 volts for 10 hours. Polyacrylamide gels were hand cast in the Hoeffer DALT multi-gel casting chamber (Amersham) at 10% Acrylamide (Bio-Rad 40% Acrylamide Solution), 2.67% piperazine diacrylamide (Bio-Rad), 0.375 M tris, pH 8.8 (Bio-Rad), 0.075% ammonium persulfate (Bio-Rad), and 0.075% TEMED (N, N, N', N'-tetramethylethylenediamine). Gels were overlaid with water-saturated butanol (Fisher), and left to polymerize at room temperature overnight.

**[0284]** Focused strips were equilibrated for ten minutes with gentle shaking in 10 milliliters Equilibration Buffer: 6 M Urea (Fisher), 50 mM tris-HCl pH 8.8 (Fisher), 30% glycerol (Fisher), 2% SDS (Fisher) with 1% dithiothreitol followed by ten minutes in Equilibration Buffer with 4% iodoacetamide.

**[0285]** The equilibrated strips were loaded onto the gel surfaces and sealed with hot agarose overlay solution containing 0.5% agarose in 50 mM tris-HCl pH 6.8, 2% SDS.

**[0286]** Gels were run in the Hoeffer DALT tank (Amersham) in 25 mM tris (Fisher), 192 mM glycine (Fisher), and 0.1% SDS overnight at 100 volts and 8°C.

**[0287]** The gels were washed three times in 500 mL Fixative (10% methanol and 7% glacial acetic acid ) for one hour each with gentle agitation. The gels were then stained overnight in 500 mL Sypro Ruby Protein Gel Stain (Molecular Probes). Gels were again washed three times in 500 mL fixative for an hour each with gentle agitation. Images were obtained on the Fluor S MultiImager (Bio-Rad) using transilluminated ultraviolet light for 45 seconds with the 520LP emission filter. Image analysis was done using PDQuest version 7.0.1 (Bio-Rad).

## **2D Gel Spot Cutting**

**[0288]** The automated gel cutting was performed using the ProteomeWorks Spot Cutter (BioRad, Hercules, CA) and PDQUEST (v.7.0.1) software. Three sets of 2D gels were cut (Table 14). Based on the gel imaging analysis, the same spots of all three gels were combined in the same well of a 96-well plate.



**Protein In-gel Digestion**

[0289] The automated digestion was performed using Investigator ProGest Digestion Station (Genomic Solutions). The sample plate (96-well pink plate) was placed onto the reaction block. A white sample collection plate was placed onto the collection block. The method used, Ruby48proGestv1, was based on the software ProGest Method Editor (v.1.1.0.29). Then the samples were digested automatically with trypsin (0.19 µg/well) at 37 °C for overnight.

**MALDI-TOF-MS Analysis**

[0290] After in-gel digestion, the digest was concentrated and desalted by using C18 reversed phase Ziptip (Millipore, Bedford, MA). Bound peptides were eluted with 4 µL matrix solution (α-cyano-4-hydroxycinnamic acid in acetonitrile/0.1%TFA 1:1 v/v).

[0291] 1 µL eluted solution was spotted onto the MALDI target. Peptide mass mapping was performed on an ABI Voyager STR matrix-assisted laser desorption/ionization (MALDI) time-of-flight mass spectrometer (Applied Biosystems, Framingham, MA). The acceleration voltage was 20 kv, the grid voltage was 14kv, the extraction delay time was 300nsec, external calibration during mass spectrometry data acquisition was used. The acquired peptide mass mapping spectra was processed and analyzed by Data Explorer software (Version 4.0.0.0.). The internal calibration was performed by using trypsin autolysis peptide mass 842.5099 and 2211.1046.

**MALDI-MS/MS Analysis**

[0292] The MALDI-MS/MS analysis was performed using API Qstar Pulsar equipped with oMALDI Source (PE Sciex). The curtain gas was 25, the declustering potential was 45, the focusing potential was set from range 220 to 250 V various by samples. CAD gas was 7 and collision energy was at 35 to 100 depending on samples. The ion energy was set at 1 kV. Data acquisition and processing was done using Analyst QS and oMALDI Server (v. 2.2) softwares. The biomaker identification was obtained with MASCOT database search using MS/MS spectra. The publically accessible link to the "MASCOT" tool for protein identification using peptide data is:

<[www.matrixscience.com/cgi/index.pl?page=/search\\_form\\_select.html](http://www.matrixscience.com/cgi/index.pl?page=/search_form_select.html)>.

**ELISA Analysis**

[0293] Reagents for human pro-Matrix Metalloproteinase 1 (pro-MMP-1) ELISA kits were obtained from R&D Systems, Inc. (Minneapolis, MN; catalog # DMP100). ELISAs were performed on conditioned media samples according to the manufacturers' instructions. The optical density of each well was determined using a universal microplate spectrophotometer ( $\mu$ Quant) from Bio-Tek Instruments, Inc. (Winooski, VT). KC-4 software from Bio-Tek Instruments, Inc. was used to extrapolate cytokine concentrations from the standard curves.

**2. Additional studies using Compound 1 – Results****2D Gel Analysis of Conditioned Media from VEGF +/- Compound 1 Treated HUVECs.**

[0294] Conditioned media isolated from HUVECs pre-treated with vehicle (DMSO) or Compound 1 (1 $\mu$ M) and subsequently stimulated with VEGF for 24 and 48 hours or baseline, untreated samples were analyzed by 2D gel analysis (see Materials and Methods). This analysis identified 1 spot (#1202) whose abundance consistently increased with addition of VEGF in two separate gel runs and appeared to decreased with Compound 1 pre-treatment, although not consistently using this technology (Table 15). These spots were excised and underwent MALDI and MALDI-MS/MS analysis for subsequent protein identification.

**Identification of Interstitial Collagenase Precursor/pro-MMP1 By Database Search Based On Peptide Mass Fingerprint Spectra.**

[0295] Peptide mass fingerprint data sets were analyzed by searching SwissProt protein database with ProteinProspector MS-Fit (Version 3.2.1). The searches were set with the following parameters, Human Mouse (Species), 1-66 kDa (molecular weight range), trypsin used for digest, maximum one missed cleavage, mass tolerance 50 ppm. Methionine was set as modified by oxidation and cysteine was set as modified by carbamidomethylation. Peptides were considered with hydrogen at N terminus and free acid at C terminus. The peptide masses were monoisotopic. The database search result was significant if the protein was ranked as the first hit and the sequence coverage was more than 30%, in addition a MOWSE score higher than 1e+003 (MS-Fit) was required. As summarized in Table 16 and

Table 17, Spot 1202 was definitively identified as interstitial collagenase precursor (pro-MMP1).

#### **ELISA Analysis of pro-MMP1 Levels in HUVEC Conditioned Media**

[0296] Because the quantitation of pro-MMP1 levels in 2D gels is only semi-quantitative (and therefore less consistent), the levels of pro-MMP-1 in HUVEC conditioned media were also assayed using a quantitative ELISA assay. The ELISA analysis indicated that levels of pro-MMP1 increase quantitatively when HUVEC cells are treated with VEGF and are decreased with pre-incubation of Compound 1 at 10nM, 100nM or 1uM concentrations (Table 18).

#### **Pro-MMP1 Levels in Plasma from Compound 1 Treated Patients in Study B**

[0297] Pro-MMP1 levels in the plasma of Study B patients after treatment with Compound 1 (day 1 pre-treatment, day 1 24 hr post-treatment, day 13 pre-treatment, day 13 12 hr post-treatment, and day 13 24 hr post-treatment) was analyzed. The results (see Table 19) demonstrate that pro-MMP1 levels increased in the plasma of patients after they received Compound 1.

**J. EXAMPLES – MORE STUDIES USING COMPOUND 1****1. More studies using Compound 1 – Materials and Methods****Plasma Samples**

[0298] All clinical plasma samples were harvested and handled in accordance with full Institutional Review Board-approved protocol, and study participants had signed the appropriate informed consent prior to any study related procedures. Plasma was separated from blood samples collected into Vacutainer tubes containing sodium heparin and shipped frozen to the SUGEN site.

[0299] Plasma samples were then thawed and centrifuged to remove particulate matter (10 min @ 5000 x g). The resulting supernatants were collected and split into aliquots and were re-frozen at –80 °C. Prior to assay, samples were thawed, Immunoglobulin Inhibiting Reagent (IIR, Bioreclamation Inc) was added to a final concentration 0.25 mg/mL, and Tween 20 was added to final concentration of 0.1%.

**Antibody chip microarray manufacture**

[0300] Glass slides were cleaned and derivatized with 3-cyanopropyltriethoxysilane. The slides were equipped with a Teflon mask, which divided the slide into sixteen 0.65 cm diameter wells or circular analysis sites called subarrays. Printing was accomplished with a Perkin-Elmer Spotarray Enterprise non-contact arrayer equipped with piezoelectric tips, which dispense a droplet (~350 pL) for each microarray spot. Antibodies were applied at a concentration of 0.5 mg/mL at defined positions. Each chip was printed with sixteen copies of one type of array, either Array 1.1 or Array 2.1 (see below). Both arrays consist of capture antibodies against different analytes and are defined by the antibody set contained. Analytes measured using both arrays are listed in Table 20.

**Array 1.1 detector set.**

| <b>Analyte</b>   | <b>Name</b>   |
|------------------|---|
| ANG              | Angiogenin  |
| BLC (BCA-1)      | B-lymphocyte chemoattractant                          |
| EGF              | Epidermal growth factor                               |
| ENA-78           | Epithelial cell-derived neutrophil-activating peptide |
| Eot              | Eotaxin   |
| Eot-2            | Eotaxin-2   |
| Fas              | Fas (CD95)  |
| FGF-7            | Fibroblast growth factor-7                            |
| FGF-9            | Fibroblast growth factor-9                            |
| GDNF             | Glial cell line derived neurotrophic factor           |
| GM-CSF           | Granulocyte macrophage colony stimulating factor      |
| IL-1ra           | Interleukin 1 receptor antagonist                     |
| IL-2 sR $\alpha$ | Interleukin 2 soluble receptor alpha                  |
| IL-3             | Interleukin 3   |
| IL-4             | Interleukin 4   |
| IL-5             | Interleukin 5   |
| IL-6             | Interleukin 6   |
| IL-7             | Interleukin 7   |
| IL-8             | Interleukin 8   |
| IL-13            | Interleukin 13  |
| IL-15            | Interleukin 15  |
| MCP-2            | Monocyte chemotactic protein 2                        |
| MCP-3            | Monocyte chemotactic protein 3                        |
| MIP-1 $\alpha$   | Macrophage inflammatory protein 1 alpha               |
| MPIF             | Myeloid progenitor inhibitory factor 1                |
| OSM              | Oncostatin M  |
| PIGF             | Placental growth factor                               |

**Array 2.1 detector set.**

| <b>Analyte</b> | <b>Name</b> |
|----------------|-------------|
|----------------|-------------|

|                |   |
|----------------|---|
| AR             | Amphiregulin  |
| BDNF           | Brain-derived neurotrophic factor                                     |
| FLT-3 Lig      | fms-like tyrosine kinase-3 ligand                                     |
| GCP-2          | Granulocyte chemotactic protein 2                                     |
| HCC4 (NCC4)    | Hemofiltrate CC chemokine 4   |
| I-309          | I-309   |
| IL-1 $\alpha$  | Interleukin 1 alpha   |
| IL-1 $\beta$   | Interleukin 1 beta  |
| IL-2           | Interleukin 2   |
| IL-17          | Interleukin 17  |
| MCP-1          | Monocyte chemotactic protein 1  |
| M-CSF          | Macrophage colony stimulating factor                                  |
| MIG            | Monokine induced by interferon gamma                                  |
| MIP-1 $\beta$  | Macrophage inflammatory protein 1 beta                                |
| MIP-1 $\gamma$ | Macrophage inflammatory protein 1 delta                               |
| NT-3           | Neurotrophin 3  |
| NT-4           | Neurotrophin 4  |
| PARC           | Pulmonary and activation-regulated chemokine                          |
| RANTES         | Regulated upon activation, normal T expressed and presumably secreted |
| SCF            | Stem cell factor  |
| sgp130         | Soluble glycoprotein 130  |
| TARC           | Thymus and activation regulated chemokine                             |
| TNF-RI         | Tumor necrosis factor receptor I                                      |
| TNF- $\alpha$  | Tumor necrosis factor alpha   |
| TNF- $\beta$   | Tumor necrosis factor beta  |
| VEGF           | Vascular endothelial growth factor                                    |

### Microarray Chip Physical Quality Measures

[0301] Each print run of microarray chips was assigned a unique Production Sheet Number, and the RCAT immunoassay run for this print run was documented. For each print run, printed slides were subjected to the following control measures: (1) two slides, one from the start and one from the end of the run, were inspected

using light microscopy. If the percentage of missing spots observed was greater than 5%, then the batch failed and the slides were discarded immediately. For all print runs described herein, 100% of the printed spots were present on slides selected for this examination; and (2) for each print run, two of the printed slides were examined by a Cy5-labeled goat-anti-mouse antibody (GAM-Cy5). Since the majority of capture antibodies in these arrays were of mouse origin, this procedure examined total antibody attachment and provided a rapid measure of surface and binding uniformity. To account for differences in binding efficiency for different capture antibodies, the intensities of all spots for each individual capture antibody were measured across the chip (4 spots/subarray, 64 spots/chip) and a %CV was calculated for that feature. The average of these %CVs for all quantified capture antibodies must be below 20% for the print batch to pass. Chips treated with GAM-Cy5 were also checked for missing spots after the assay and if the percentage of missing spots was greater than 5%, then the batch failed (for these studies 100% of the printed spots were still present after this assay). Following these QC measures, qualified slides were stored at 4°C until used.

### **Reagent Quality Control Measures**

[0302] The assay suite was considered as consisting of the microarray chips, detector antibodies and the reagents required for the RCAT portion of the assay. There were validation procedures for these reagents individually as well as a functional validation of the entire set. Reagents used in the RCA portion of the assay were from reserved vendor lots where possible. Materials produced in-house were subjected to QC procedures and qualified on microarray chips before release. If lot numbers changed for a particular reagent that is supplied by an outside vendor, the new lots were qualified by comparison with existing qualified stocks.

[0303] For each array type, a concentrated batch of detectors was prepared which consisted of a mixture of biotinylated antibodies directed against all analytes represented by an array. A functional QC was then performed for each detector antibody batch by carrying out the standard RCAT assay on a specially prepared sample set. Mixtures of 2-3 different cytokines were prepared so as to provide a high intensity signal and applied to 14 wells of a chip (with each well being treated with a different mixture up to the total complement of detector antibodies) and two arrays

were used as blank controls. The chips were developed and scanned and the resulting signals were compared to the positional map of the particular array. This examination demonstrated that the stock detector mixture was complete and the features were active. Once a detector batch had passed this QC, it was distributed into smaller volumes and released for use in the assay.

### **Positional and Functional Quality Measures**

[0304] Following printing, a set of microarray chips was validated in concert with the qualified reagents discussed above. This was a two-part quality control measure. The first portion was identical to the detector antibody qualification procedure just described. In this case, the high intensity signals were compared to the array map and the proper positioning of capture antibody replicates was verified. The second test was a functional QC for all analytes of a specified array using known sample matrices. Normal human serum (Jackson ImmunoResearch Laboratories, Code#009-000-121) and heparinized plasma were assayed neat or spiked with purified recombinant cytokines representing all analytes in the array. Spiked mixtures were then titrated down the subarrays of a slide from 5,000 pg/ml to 20 pg/mL of spiked cytokine concentrations along with three subarrays for each un-spiked control sample. The data was quantified and for every analyte in the array a titration curve was generated to show that the feature intensity was above background and exhibiting increasing intensity with increasing analyte concentrations.

### **RCA Immunoassay**

[0305] Prior to assay, the slides were removed from storage at room temperature in sealed containers and opened in a humidity controlled chamber (35-40%). Blocking was done by submerging the slides in a Coplin jar filled with blocking buffer (Seablock, Pierce Chemical Co., 1:1 dilution with 1X PBS) pre-chilled to 4°C, and placing the Coplin jar in a 37°C incubator for 1 hour. The slides were then washed twice (2 min per wash) in 60 mL of 1x PBS/0.5% Brj-35 washing buffer. On each slide, control serum (Jackson ImmunoResearch Laboratories) was applied to one subarray, plasma control applied to two subarrays, and a negative control with PBS buffer applied to two subarrays. The test samples were assayed on the remaining 11 subarrays. Twenty microliters of the treated sample were then



applied to each subarray. The basics of performing immunoassays with RCA signal amplification has been described (*Nat. Biotechnol.* (2002) 20:359-65) and we are using SOPs derived from the protocols used in that study. Slides were scanned (GenePix 4000B, Axon Instruments Inc.) at 10  $\mu\text{m}$  resolution with a laser setting of 100% and a PMT setting of 550 V. Mean pixel fluorescence values were quantified using the fixed circle method in GenePix Pro 4.0 (Axon Instruments). Using proprietary software, the fluorescence intensity of microarray spots was analyzed for each feature and sample, and the resulting mean intensity values were determined. Dose-response curves for selected cytokines were examined, ensuring that feature intensity is above background and exhibiting increasing intensity with increasing analyte concentration.

### **ELISA Analysis**

[0306] Reagents for FLT3 ligand (FL) and IL-6 ELISA kits were obtained from R&D Systems, Inc. (Minneapolis, MN; catalog #s DFK00, Q6000). C-reactive protein (CRP) (accession ID AAA 52075) ELISA kits were obtained from KMI Diagnostics (Minneapolis, MN; catalog #EU59131). ELISAs were performed on patient plasma according to the manufacturers' instructions. The FL and CRP kits relied on a colorimetric readout; the optical density of each well was determined using a microplate spectrophotometer and data was analyzed using KC-4 software from Bio-Tek Instruments, Inc. The IL-6 kit was a chemiluminescent sandwich ELISA; luminescence values were determined on a microplate luminometer. SOFTmaxPRO software was used to extrapolate cytokine concentrations from the standard curves.

## **2. More studies using Compound 1 – Results**

### **Plasma markers identified using Antibody chip technology**

[0307] A multiplex antibody chip based approach (MSI, Molecular Staging Inc.) was used to identify plasma biomarkers of compound 1. Plasma samples harvested from 3 advanced malignancy patients pre and post Compound 1 treatment (Phase I trial A) were used for this analysis. Twenty three of 108 markers tested, showed changes following Compound 1 treatment (day 28). These are listed in Table 21. Controls included normal donor plasma which did not show significant changes

in these markers. Each of these is a potential biomarker of Compound 1, and may reflect drug exposure, biological activity or efficacy.

[0308] A number of markers showing the most dramatic changes and/or of known biological significance were further investigated (specifically VEGF, PLGF, IL-6, IL-8 and MCP-1). The relative changes were validated by ELISA on the same patient samples assessed in the antibody chip screen, and both methods showed good concordance (Table 22). Several of these markers had previously been identified by ELISA analysis on compound 1 treated samples, (PLGF, VEGF, IL-6), and several were novel (FLT3 ligand and MCP-1). Additional data on FLT3 ligand levels tested in an expanded set of patients is provided in Figure 25. Dramatic induction was observed following Compound 1 treatment in all cases.

#### **Plasma ELISA Studies**

[0309] In an effort to identify novel biomarkers of exposure to Compound 1, plasma samples were analyzed from 18 patients enrolled in Trial B. Plasma was taken both before study (D1 PRE) as well as at the end of the first cycle of treatment (Day 28 POST). Each time point was measured in triplicate and the standard deviation from the mean was calculated. Both the mean value and standard deviation for each patient at each time point is shown graphically in Figure 25. It was found that 100% of the patients exhibited an increase in FLT3 ligand (FL) concentration from day 1 to day 28. In 14 out of 18 patients, the increase was more than four-fold. The increase in FLT3 ligand concentration is attributed to treatment with Compound 1.

#### **Plasma ELISA Studies – Fatigue Corrolation**

[0310] To find biomarkers that correlated with fatigue, plasma samples were analyzed from 62 patients enrolled in trials for Compound 1. Samples were taken before study (D1) and either two or four weeks after the start of cycle 1 dosing (Day 13 for trials B, C and D and Day 28 for A and E). The patients are grouped according to their highest recorded fatigue grade (0-4 scale from the NCI Common Toxicity Criteria). As seen in Figure 26, there is a statistically significant difference between the increases in IL-6 seen in patients with low fatigue (Grade 1 or 0) and those with

moderate to high fatigue (Grade 3 or 4),  $p=0.001$ . Thus, a patient who exhibits a large change in IL-6 plasma concentration (greater than two-fold) after treatment with Compound 1 has a much higher chance of experiencing a high degree of fatigue (Grade 3 or 4) than a patient whose IL-6 level remains more stable.

[0311] Plasma samples were further analyzed from 18 patients enrolled in Trial B for Compound 1. Samples were taken before study (D1) and two weeks after the start of cycle 1 dosing (D13). As shown with IL-6 levels, the patients are grouped according to their highest recorded fatigue grade (0-4). See Figure 27. It was determined there is a statistically significant difference in C-reactive protein (CRP) (accession ID AAA 52075) induction between patients with little fatigue (Grade 0, 1, or 2) and those with moderate to severe fatigue (Grade 3 or 4),  $p = 0.0088$ . Therefore, patients with a greater than two-fold increase in C-reactive protein after treatment with Compound 1 are more prone to experiencing high fatigue than those who have smaller fold changes in CRP.

#### **Plasma ELISA Studies –Corrolation to biological response and/or clinical efficacy**

[0312] Levels of C-reactive protein were measured as described above for the experiments involving CRP and fatigue. ELISAs were performed on plasma samples from patients before treatment (i.e., baseline values). The patients' samples and results were divided into two groups based upon observed clinical outcome. Patients with stable disease (SD pts) were defined as patients on study for over 6 months. Patients with progressive disease (PD pts) were defined as patients who had come off study due to disease progression or lack of efficacy in fewer than 6 months. This separation of patients demonstrated that patients with progressive disease had much higher baseline levels of CRP than those patients who were stable (median values of 63.8  $\mu\text{g/mL}$  vs. 6.5  $\mu\text{g/mL}$ , respectively) (Figure 28). If a patient were to have a baseline level of CRP of above 20  $\mu\text{g/mL}$  before treatment, that patient has a greater chance of rapidly progressing than if the level of CRP were below 20  $\mu\text{g/mL}$ . Thus, CRP is a baseline marker of biological response and/or clinical efficacy.

**K. EXAMPLES – COMPOUND 1 STUDIES OF OB-CADHERIN 1 PROTEIN****1. Compound 1 studies of OB-cadherin 1 protein – Materials and Methods****Tumor samples**

[0313] Colo205 human colon xenograft tumors were isolated and fixed in Streck Tissue Fixative (Streck Laboratories, Inc., La Vista, NE). Samples used in immunohistochemistry were sent out to BioPathology Sciences Medical Corporation (South San Francisco, CA) for paraffin embedding and sectioning.

**Antibodies**

[0314] A rabbit polyclonal antibody recognizing the cytoplasmic tail region of OB-cadherin 1 (cadherin 11) was purchased from Zymed Laboratories, Inc. (Zymed reagent #71-7600; South San Francisco, CA).

**Immunohistochemistry**

[0315] Sections (4-5  $\mu$ m) stained using an automated immunohistochemistry system (Benchmark System, Ventana Medical Systems, Inc., Tucson, Arizona). In brief, slides were deparaffinized using heat at 75°C and Ventana's EZ Prep product (Ventana reagent #950-102). Antigen retrieval was performed by incubating the slides for 30 min with Ventana's CC2 product (Ventana reagent #950-123), a citrate-based solution with pH 6.0. Primary antibody (5  $\mu$ g/ml) was incubated for 24 min at room temperature, followed by a secondary detection system, using biotinylated secondary antibody (Vector anti-rabbit secondary, BA-1000, at 2.5  $\mu$ g/ml; Vector Laboratories, Burlingame, CA) with incubation time of 8 min. Streptavidin-horseradish peroxidase with 3, 3' diaminobenzidine as a substrate were used in conjunction with the secondary detection system. All samples analyzed for OB-cadherin 1 expression were also stained with the omission of primary antibody as a negative control.

## **2. Compound 1 studies of OB-cadherin 1 protein – Data Summary**

**[0316]** As expression of OB-cadherin 1 (cadherin 11) RNA was found to be up-regulated at 24 hour post-Compound 1 treatment (see Table 12), effects on OB-cadherin 1 expression at the protein level was also examined. Colo205 xenograft tumors were isolated from Compound 1-treated mice at 24 and 48 hours post treatment. Tumors were fixed in formalin and sections were isolated and processed for immunohistochemistry (IHC).

**[0317]** Tissue sections were stained with an antibody that recognizes OB-cadherin 1. As a negative control, adjacent sections were processed similarly but with the omission of a primary antibody. This analysis identified up-regulation of OB-cadherin 1 protein in Colo205 tumors treated with Compound 1 for 24 and 48 hours as compared to vehicle treated samples (Figure 29).

**TABLES****Table 1.**

|                | Number of samples<br>from which RNA<br>was processed | Number with RNA<br>yield >1ug, at both<br>d1 and d56 | Number<br>hybridized to<br>U95A chips | Number for which<br>data passed Quality<br>Control inspection<br>for further analysis |
|----------------|--|--|---------------------------------------|---|
| <b>SU5416</b>  |  |  |                                       |   |
| CR             | 0  | 0  | 0                                     | 0   |
| PR             | 13   | 8  | 6                                     | 6*  |
| MR             | 6  | 3  | 2                                     | 1   |
| SD             | 6  | 5  | 1                                     | 1   |
| PD             | 10   | 7  | 6                                     | 5*  |
| <b>Control</b> |  |  |                                       |   |
| CR             | 1  | 1  | 1                                     | 1*  |
| PR             | 9  | 5  | 5                                     | 5*  |
| MR             | 4  | 1  | 1                                     | 0   |
| SD             | 3  | 2  | 2                                     | 2   |
| PD             | 11   | 9  | 7                                     | 6*  |
| Total:         | 63   | 41   | 31                                    | 27  |

**\* These samples were included in the dataset used in detailed analysis**

**Table 2.**

| <u>Affymetrix<br/>number</u> | <u>Gene name/<br/>Symbol</u>    | <u>Putative function(s)</u>                           | <u>Increased in<br/>SU5416 arm</u> | <u>Increased in<br/>Control arm</u> |
|------------------------------|---------------------------------|---|------------------------------------|-------------------------------------|
| 34546_at                     | Defensin $\alpha$ 4             | Corticostatic, Ca channel<br>regulator                | 10 of 11                           | 6 of 12                             |
| 33530_at                     | CEA CAM 8                       | Tumor antigen, integral membrane<br>protein.          | 9 of 11                            | 4 of 12                             |
| 37054_at                     | BPI                             | Anti-pathogen response                                | 9 of 11                            | 4 of 12                             |
| 31859_at                     | MMP-9                           | Protease; ECM maintenance                             | 8 of 11                            | 2 of 12                             |
| 32821_at                     | Lipocalin 2                     | Anti-pathogen response; apoptosis                     | 10 of 11                           | 5 of 12                             |
| 34319_at                     | S100 P                          | Ca-binding protein                                    | 9 of 11                            | 3 of 12                             |
| 41249_at                     | Hypothetic. Protein<br>FLJ13052 | unknown   | 7 of 11                            | 1 of 12                             |
| 1962_at                      | Liver arginase                  | Amino acid metabolism                                 | 9 of 11                            | 3 of 12                             |
| 266_s_at                     | CD24 antigen                    | Anti-pathogen response;<br>differentiation of B cells | 9 of 11                            | 0 of 12                             |
| 31506_s_at                   | Defensin $\alpha$ 3             | Chemotaxis; anti-microbial<br>response                | 10 of 11                           | 4 of 12                             |
| 32275_at                     | Antileuko-protease              | Secreted inhibitor of serine<br>proteases             | 9 of 11                            | 4 of 12                             |
| 115_at                       | Thrombospondin 1                | Blood clotting; angiogenesis                          | 9 of 11                            | 3 of 12                             |
| 37149_s_at                   | Lactoferrin                     | Iron transport; putative protease                     | 11 of 11                           | 5 of 12                             |

**Table 3.**

| <u>Gene</u>         | <u>Forward Primer</u>                       | <u>Reverse Primer</u>                           |
|---------------------|---|---|
| Thrombospondin 1    | TTGGCTACCAGTCCAGCAGC<br>(SEQ ID NO: 1)      | GGGTTGGTGTCCTCAGTAGGA<br>(SEQ ID NO: 2)         |
| MMP-9               | CCCGGAGTGAGTTGAACCA<br>(SEQ ID NO: 3)       | CCTAGTCCTCAGGGCACTGC<br>(SEQ ID NO: 4)          |
| Defensin $\alpha$ 3 | CCCAGAAGTGGTTGTTTCCT<br>(SEQ ID NO: 5)      | GTCCATGTTTTTCCTTGAGCCT<br>(SEQ ID NO: 6)        |
| Lactoferrin         | CTGGAAGCCTGTGAATTCC<br>(SEQ ID NO: 7)       | GAATGGCTGAGGCTTTCTTGG<br>(SEQ ID NO: 8)         |
| Lipocalin-2         | GCTGACTTCGGAACATAAAGGAGAA<br>(SEQ ID NO: 9) | TGGGACAGGGAAGACGATGT<br>(SEQ ID NO: 10)         |
| CD24                | CTGCCTCGACACACATAAACCTT<br>(SEQ ID NO: 11)  | CATCTAAGCATCAGTGTGTGACC<br>A<br>(SEQ ID NO: 12) |

**Table 4.**

| <u>P-value of Mann-Whitney U Test</u> |                               |                                      |
|---------------------------------------|-------------------------------|--------------------------------------|
| <u>Gene</u>                           | <u>Affymetrix</u><br>(n = 23) | <u>SYBR Green RT-PCR</u><br>(n = 31) |
| MMP-9                                 | 0.0025                        | 0.0748                               |
| Thrombospondin 1                      | 0.0267                        | 0.7186                               |
| CD24                                  | 0.0006                        | 0.0057                               |
| Defensin $\alpha$ 3                   | 0.0002                        | 0.2196                               |
| Lactoferrin                           | 0.0002                        | 0.0065                               |
| Lipocalin-2 (LCN2)                    | 0.0005                        | 0.0057                               |



**Table 5.**

| Gene        | n  | Rank Sum<br>(Treatment) | Rank Sum<br>(Control) | Mann-Whitney U | p-value |
|-------------|----|-------------------------|-----------------------|----------------|---------|
| MMP-9       | 36 | 415                     | 251                   |                | 0.0095  |
| CD24        | 36 | 443                     | 223                   |                | 0.0005  |
| Lactoferrin | 36 | 460                     | 206                   |                | 0.0001  |
| LCN2        | 36 | 419                     | 247                   |                | 0.0065  |

**Table 6.****Predictor Gene Set for discriminating between the control and Compound B arms: LCN2, CD24, Lactoferrin**

## 1. All cases pooled (67 cases from both trials)

|           | Control | Treatment | % Correct |
|-----------|---------|-----------|-----------|
| Control   | 26      | 5         | 84        |
| Treatment | 6       | 30        | 83        |
| Total     | 32      | 35        | 84        |

## 2. Jackknifed classification matrix for all cases pooled (67 cases from both trials)

|           | Control | Treatment | % Correct |
|-----------|---------|-----------|-----------|
| Control   | 26      | 5         | 84        |
| Treatment | 8       | 28        | 78        |
| Total     | 34      | 33        | 81        |

## 3. Prediction subset (randomly selected 34 cases) from all cases pooled (67 cases in both trials)

|           | Control | Treatment | % Correct |
|-----------|---------|-----------|-----------|
| Control   | 13      | 1         | 93        |
| Treatment | 4       | 16        | 80        |
| Total     | 17      | 17        | 85        |

## 4. Validation subset (randomly selected 33 cases) from all cases pooled (67 cases in both trials)

|           | Control | Treatment | % Correct |
|-----------|---------|-----------|-----------|
| Control   | 11      | 6         | 65        |
| Treatment | 5       | 11        | 69        |
| Total     | 16      | 17        | 67        |

Table 7.

## Trial C patients 1-23 PLGF plasma level ratios

| <u>Patient #</u> | <u>d1 (6 hr):d1 (0 hr)</u> | <u>d29:d1</u>   | <u>d42:d1</u>   |
|------------------|----------------------------|-----------------|-----------------|
| 1                | 0.695512                   | 1.871238        | 0.398897        |
| 2                | 2.050289                   | 11.96579        | 1.040025        |
| 3                | 1.965517                   | 3.586207        | 1.206897        |
| 4                | 1.985061                   | 24.72922        | 1.985061        |
| 5                | 1.09557                    | 11.3316         | 1.09557         |
| 6                | 1.800672                   | 11.02117        | 1.365586        |
| 8                | 1.16493                    | 12.38985        | 1.157115        |
| 10               | 1.622462                   | >10             | 2.652309        |
| 11               | 1.250022                   | 7.511615        | 1.386382        |
| 13               | 1.038442                   | 1.817441        | NA              |
| 15               | 0.896403                   | 6.651554        | 1.189041        |
| 17               | 0.907692                   | 19.21308        | 1.134385        |
| 18               | 1.007357                   | 12.30822        | 1.105295        |
| 20               | 1.2261                     | 11.29078        | 1.598445        |
| 21               | 1.518564                   | 14.84205        | 0.955559        |
| 22               | 1                          | 2.423462        | 0.815385        |
| <b>Average</b>   | <b>1.326537</b>            | <b>10.19689</b> | <b>1.272397</b> |

\*\*\*Note: d15:D1 ratio is 6.4 for pt. 13

Table 8.

| <u>MIG</u>     |              |               |                      |              | <u>IP-10</u> |                      |              |
|----------------|--------------|---------------|----------------------|--------------|--------------|----------------------|--------------|
| <u>Patient</u> | <u>day 1</u> | <u>day 15</u> | <u>end C1 dosing</u> | <u>Ratio</u> | <u>day1</u>  | <u>end C1 dosing</u> | <u>Ratio</u> |
| 11 (B)         | 41.927       |               | 739.71               | 17.64281     | 55.617       | >500                 | >9           |
| 1              | 48.375       |               | 1066.2               | 22.04031     | 64.847       | >500                 | >7.7         |
| 11             | 34.432       |               | 344.93               | 10.01772     | 65.32        | 384.06               | 5.879669     |
| 17             | 166.8        |               | 907.09               | 5.438189     | 72.29        | >500                 | >6.9         |
| 24             | 80.751       |               | 314.2                | 3.890973     |              |                      |              |
| 26             | 80.751       |               | 995.47               | 12.32765     | 64.296       | >500                 | >7.7         |
| 27             | 80.826       |               | 81.439               | 1.007584     |              |                      |              |
| 7              | 106.04       |               | 145.64               | 1.373444     | 139.2        | 240.31               | 1.726365     |
| 20             | 161.91       |               | 698.23               | 4.312458     | 73.67        | >500                 | >6.9         |
| 22             | 37.685       | 339.16        |                      | 8.999867     |              |                      |              |
| 9 (A)          | 60.393       |               | 138.56               | 2.294306     |              |                      |              |

| <u>I-TAC</u>   |              |               |                      |              |
|----------------|--------------|---------------|----------------------|--------------|
| <u>Patient</u> | <u>day 1</u> | <u>day 15</u> | <u>end C1 dosing</u> | <u>Ratio</u> |
| 11 (B)         | 428.83       |               | >4000.0              | >9           |
| 1              |              |               |                      |              |
| 11             |              |               |                      |              |
| 17             |              |               |                      |              |
| 24             | 259.38       |               | 771.04               | 2.972627     |
| 26             | 97.917       |               | 701.46               | 7.163822     |
| 27             | 139.94       |               | 315.69               | 2.255895     |
| 7              |              |               |                      |              |
| 20             |              |               |                      |              |
| 22             | 190.76       | 2020.2        |                      | 10.59027     |
| 9 (A)          | 59.975       |               | 212.26               | 3.539141     |

Table 9.

| <u>Patient #</u> | <u>PLGF Ratio (end dosing:d1)</u> | <u>VEGFR2 ratio (end dosing:d1)</u> | <u>Primary Diagnosis</u> |
|------------------|-----------------------------------|-------------------------------------|--------------------------|
| Trial C          |                                   |                                     |                          |
| 1                | 1.871237941                       | 0.265856292                         | Synovial Sarcoma         |
| 2                | 11.96579454                       | 0.25171334                          | Rectal                   |
| 3                | 3.586206897                       | 0.5673112                           | Gall-bladder             |
| 4                | 24.72921991                       | 0.34236691                          | Hepatocellular           |
| 5                | 11.33159926                       | 0.406890612                         | Melanoma                 |
| 6                | 11.02116835                       | 0.572980623                         | Breast                   |
| 7                | 23.86685363                       | 0.404286499                         | Ovary                    |
| 8                | 12.38984817                       | 0.318366334                         | Small Cell Lung          |
| 10               | 10                                | 0.45614753                          | Melanoma                 |
| 11               | 7.511615487                       | 0.323681006                         | Met. Colon               |
| 13               | 1.817440506                       | 0.460416464                         | Renal Cell Carcinoma     |
| 14               | 3.080408542                       | 0.575703582                         | Met. Melanoma            |
| 15               | 6.651553529                       | 0.506347193                         | Renal Cell Carcinoma     |
| 17               | 19.21307692                       | 0.177452364                         | NSCLC                    |
| 18               | 12.30822285                       | 0.271285002                         | NSCLC                    |
| 20               | 11.29078149                       | 0.385479698                         | Colon                    |
| 21               | 14.84205128                       | 0.369637606                         | Breast                   |
| 22               | 2.423461538                       | 0.479139734                         | Sarcoma                  |
| 23               | 1                                 | 0.504789782                         | Sarcoma                  |
| 24               | 0.99016936                        | 0.457140878                         | met. Rectal carcinoma    |
| 25               | 12.03862173                       | 0.250133543                         | Retropero Sarcoma        |
| 26               | 13.29469461                       | 0.493391074                         | Met Pelvis Sarcoma       |
| 29               | 5.237072177                       | 0.59927457                          | SCCR R) Parotid          |
| 30               |                                   | 0.519969363                         | Colon AdenoCA            |
| 31               |                                   | 0.330647033                         | Lung AdenoCA             |
| Trial A          |                                   |                                     |                          |
| 1                |                                   | 0.565173104                         | Renal Cell Carcinoma     |
| 3                |                                   | 0.597994214                         | Bronchial adeno.         |
| 4                |                                   | 0.685465839                         | breast carcinoma         |
| 5                | 12.97391648                       | 0.182557005                         | uterine                  |
| 6                | 25.082632                         | 0.458079657                         | pelvic angiosarcoma      |
| 7                |                                   | 0.648790016                         | pleural mesothelioma     |
| 8                |                                   | 0.64392508                          | uterine                  |
| 9                |                                   | 0.38520981                          | Bronchial adeno.         |
| 10               | 5.301660143                       | 0.44915001                          | colorectal               |
| 13               |                                   | 0.297438475                         | neuroendocrine           |

**Table 9. cont.**

| <u>Patient #</u> | <u>PLGF Ratio (end dosing:d1)</u> | <u>VEGFR2 ratio (end dosing:d1)</u> | <u>Primary Diagnosis</u> |
|------------------|-----------------------------------|-------------------------------------|--------------------------|
| Trial D          |                                   |                                     |                          |
| 1                |                                   | <i>0.502083475</i>                  | GIST                     |
| 3                | 2.98130415                        | <i>0.670742516</i>                  | GIST                     |
| 4                | <i>5.228142589</i>                | 0.972905837                         | GIST                     |
| 5                | 1.351061278                       | <i>0.616277438</i>                  | GIST                     |
| 6                | <i>7.055260831</i>                | <i>0.684932856</i>                  | GIST                     |
| 13               | <i>4.095209935</i>                | <i>0.600072917</i>                  | GIST                     |
| 14               | <i>4.786806356</i>                | <i>0.685754939</i>                  | GIST                     |
| 15               | <i>22.29951691</i>                | 0.767346939                         | GIST                     |
| 16               | <i>3.034877351</i>                | 0.727153597                         | GIST                     |
| 18               | <i>16.89889246</i>                | <i>0.471077781</i>                  | GIST                     |
| 19               | 2.782095462                       | <i>0.542935245</i>                  | GIST                     |
| 20               | <i>12.47129736</i>                | <i>0.598602839</i>                  | GIST                     |
| 21               | <i>11.56450225</i>                | <i>0.351218422</i>                  | GIST                     |
| 22               | 2.996492067                       | <i>0.644054653</i>                  | GIST                     |
| Trial B          |                                   |                                     |                          |
| 4                |                                   | <i>0.67109839</i>                   | Head & Neck              |
| 5                |                                   | <i>0.678411145</i>                  | CRC                      |
| 6                |                                   | <i>0.4130696</i>                    | thymic                   |
| 7                |                                   | <i>0.301532905</i>                  | CRC                      |
| 8                |                                   | <i>0.456886687</i>                  | thyroid                  |
| 9                |                                   | <i>0.597322954</i>                  | thyroid                  |

Table 10.

| <u>MIG</u>       |              |               |                      |              |                    |
|------------------|--------------|---------------|----------------------|--------------|--------------------|
| <u>Patient #</u> | <u>day 1</u> | <u>day 15</u> | <u>end C1 dosing</u> | <u>Ratio</u> | <u>Cancer Type</u> |
| 11 (B)           | 41.927       |               | 739.71               | 17.64281     | Pancreatic         |
| 1                | 48.375       |               | 1066.2               | 22.04031     | Synovial Sarcoma   |
| 11               | 34.432       |               | 344.93               | 10.01772     | Met. Colon         |
| 17               | 166.8        |               | 907.09               | 5.438189     | NSCLC              |
| 24               | 80.751       |               | 314.2                | 3.890973     | Met. Rectal        |
| 26               | 80.751       |               | 995.47               | 12.32765     | Pelvis Sarcoma     |
| 20               | 161.91       |               | 698.23               | 4.312458     | Colon              |
| 22               | 37.685       | 339.16        |                      | 8.999867     | Sarcoma            |
| 9 (A)            | 60.393       |               | 138.56               | 2.294306     | Bronchial Adeno.   |

Table 11A.

| Transcript Name                          | Putative Role  | Accession No. | Time Point (hrs) | Fold Change Increase |
|--|--|---------------|------------------|----------------------|
| Basic transcription factor 3 homologue   | Transcription factor                                 | M90354        | 6                | 2.1                  |
| c-jun proto oncogene                     | Transcription factor                                 | J04111        | 6                | 2.5                  |
| c-fos cellular oncogene                  | Transcription factor                                 | K00650        | 6                | 4.2                  |
| Tyrosine phosphatase non-receptor type 2 | Protein phosphatase                                  | NM_080422     | 6                | 2.2                  |
| cdc2-related protein kinase              | Cell cycle regulation                                | M68520        | 6                | 19                   |
| Cyclin C                                 | Cell cycle regulation                                | M74091        | 6                | 2.5                  |
| DNA polymerase gamma                     | DNA polymerase                                       | U60325        | 6                | 7.3                  |
| Basic transcription factor 3 homologue   | Transcription factor                                 | M90354        | 24               | 2.2                  |
| Protein kinase C alpha                   | Protein kinase                                       | X52479        | 24               | 3.0                  |
| Lipocortin II/annexin A2                 | Ca <sup>++</sup> -regulated membrane binding protein | D00017        | 24               | 2.3                  |
| Histone H2B, member R                    | Transcriptional regulation                           | AF531293      | 24               | 3.0                  |
| Amphiregulin                             | Growth factor  | NM_001657     | 24               | 6.1                  |



Table 11A cont.

| Transcript Name                                       | Putative Role                                     | Accession No.   | Time Point (hrs) | Fold Change Decrease |
|---|---|---|------------------|----------------------|
| Ephrin receptor EphB4                                 | Tyrosine kinase receptor                          | NM_004444   | 6                | 2.5                  |
| Hanukah factor/Granzyme A                             | Serine protease                                   | M18737  | 24               | 2.3                  |
| von Hippel-Lindau (VHL) tumor suppressor              | Tumor suppressor                                  | NM_000551   | 24               | 3.7                  |
| OB-cadherin 1   | Ca <sup>++</sup> -dependent cell adhesion protein | D21254  | 24               | 2.2                  |
| OB-cadherin 2   | Ca <sup>++</sup> -dependent cell adhesion protein | D21255  | 24               | 2.0                  |
| Phosphoinositol 3-phosphate-binding protein-3 (PEPP3) | Phosphoinositide-binding protein                  | NM_014935   | 24               | 2.1                  |
| Phosphoinositol 3-kinase, p85 subunit                 | Proliferation                                     | M61906  | 24               | 2.2                  |
| Mucin 1   | Adhesion, cell-cell interaction                   | J05582  | 24               | 2.5                  |
| Hepatitis C-associated microtubular aggregate p44     | Interferon-induced protein                        | Exon 1-9<br>D28908, D28909,<br>D28910, D28911,<br>D28912, D28913,<br>D28914, D28915 | 24               | 2.0                  |
| ErbB3/HER3 receptor tyrosine kinase                   | Growth factor receptor                            | M29366  | 24               | 2.1                  |

Table 11B.

| Transcript Name                        | Putative Role         | Accession No. | Time Point (hrs) | Fold Change Increase |
|--|-----------------------|---------------|------------------|----------------------|
| Vinculin                               | Cell adhesion         | M33308        | 4                | 2.5                  |
| Basic transcription factor 3           | Transcription factor  | M90357        | 24               | 2.2                  |
| Phosphoinositol 3-kinase, p110 subunit | Proliferation         | NM_006219     | 24               | 4.5                  |
| Transcript Name                        | Putative Role         | Accession No. | Time Point (hrs) | Fold Change Decrease |
| Gelsolin                               | Actin binding protein | X04412        | 4                | 2.1                  |
| Cyclin D2                              | Transcription         | NM_001759     | 4                | 2.2                  |

Table 12.

| Transcript Name                        | Accession No. | Relative Expression Level (6 hr) | Relative Expression Level (24 hr) |
|--|---------------|----------------------------------|-----------------------------------|
| Amphiregulin                           | NM_001657     | 1.9                              | 2.5                               |
| Cdc2-related protein kinase            | M68520        | 0.43                             | 0.55                              |
| Phosphoinositol 3-kinase, p110 subunit | NM_006219     | 0.59                             | 1.6                               |
| Cyclin C                               | M74091        | 842                              | 223                               |
| OB-cadherin 1                          | D21254        | 0.35                             | 23.8                              |
| OB-cadherin 2                          | D21255        | 0.40                             | 0.51                              |
| Phosphoinositol 3-kinase, p85 subunit  | M61906        | 1.0                              | 230                               |
| Mucin 1                                | J05582        | 0.32                             | 1.13                              |
| von Hippel-Lindau tumor suppressor     | NM_000551     | 0.9                              | 0.55                              |
| Ephrin receptor, EphB4                 | NM_004444     | 3.5                              | 3.1                               |
| Gelsolin                               | X04412        | 4.0                              | 0.04                              |

Table 13.

| Transcripts              | GenBank<br>Accession No. | Forward Primer (5' - 3')                                | Reverse Primer (5' - 3')                            | Taqman Probe (5' - 3')                             |
|--------------------------|--------------------------|---|---|--|
| Amphiregulin             | NM_001657                | ATGATGAGTCGTCCTCT<br>TTCC<br>(SEQ ID NO: 13)            | TGACAATTGAAAGTTTAA<br>AACCATCAT<br>(SEQ ID NO: 14)  | TCCATTGTCTTATGA<br>TCCAC<br>(SEQ ID NO: 15)        |
| CDK-2 related<br>protein | M68520                   | AGTTAGAAAGTTAGGGTTT<br>AGGCATCAAT<br>(SEQ ID NO: 16)    | TACCCATGCCCTCACTCA<br>ATC<br>(SEQ ID NO: 17)        | AAGTGTGAGCAATTCT<br>CAA<br>(SEQ ID NO: 18)         |
| PI3-kinase,<br>p110      | NM_006219                | CCAGTGTGTGAGGATGC<br>ATATC<br>(SEQ ID NO: 19)           | CAGTCAACATCAGCGCAA<br>AGA<br>(SEQ ID NO: 20)        | ATTCCCATGCCGTCG<br>TA<br>(SEQ ID NO: 21)           |
| PI3-kinase, p85          | M61906                   | CAAACCTACTGTATCTCT<br>AATACAGTGTGACT<br>(SEQ ID NO: 22) | GACAGAGATGATTATCCC<br>TTTAAACCA<br>(SEQ ID NO: 23)  | AGCGCTCACCTTTG<br>(SEQ ID NO: 24)                  |
| Cyclin C                 | M74091                   | CCTACAGACAGACATACA<br>TAGACATTTCAA<br>(SEQ ID NO: 25)   | ATTATGCTTCATGTTTCCT<br>GGCTTA<br>(SEQ ID NO: 26)    | CCAAATTAAGAAAT<br>ATTATACTAATCA<br>(SEQ ID NO: 27) |
| OB-cadherin 1            | D21254                   | GACAACAGTTCTGAGCTG<br>TAATTTCG<br>(SEQ ID NO: 28)       | TGGGTTAAAGCTGGCTGA<br>ATATTAT<br>(SEQ ID NO: 29)    | ACTCTGGACACTCTA<br>TATGT<br>(SEQ ID NO: 30)        |
| OB-cadherin 2            | D21255                   | TCAGCCAGCTTAAACCCA<br>TACAA<br>(SEQ ID NO: 31)          | TGGCACGTATTAGTTAA<br>GATGAAAGTAG<br>(SEQ ID NO: 32) | CTTGTTACTGCTGAT<br>TCT<br>(SEQ ID NO: 33)          |
| Mucin 1                  | J05582                   | TTCAGAGGCCCCACCAAT<br>T<br>(SEQ ID NO: 34)              | CCCACATGAGCTTCCACA<br>CA<br>(SEQ ID NO: 35)         | TCTCGGACACTTCTC<br>(SEQ ID NO: 36)                 |

Table 13 cont.

| Transcripts             | GenBank<br>Accession No. | Forward Primer (5' - 3')                          | Reverse Primer (5' - 3')                          | Taqman Probe (5' - 3')                       |
|-------------------------|--------------------------|---|---|--|
| VHL tumor<br>suppressor | NM_000551                | TGAGGCAGGGACAAAGTCT<br>TTCT<br>(SEQ ID NO: 37)    | ACCCTGACTGAAGGCTCA<br>TGA<br>(SEQ ID NO: 38)      | CTCTTTGAGACCCCA<br>GTGC<br>(SEQ ID NO: 39)   |
| EphB4                   | NM_004444                | TCTACCGTCCTTGTCATA<br>ACTTTGTG<br>(SEQ ID NO: 40) | ATGATGATGGGCCCCCTGT<br>T<br>(SEQ ID NO: 41)       | CCTTTGCCCCAAGTTG<br>(SEQ ID NO: 42)          |
| Gelsolin                | X04412                   | TGGACGTTTTTGATCGA<br>AGAG<br>(SEQ ID NO: 43)      | AAGTCAAGGCTTCTGTCT<br>TTTCTTCT<br>(SEQ ID NO: 44) | CTTGAGAAATCCTTTC<br>CAACC<br>(SEQ ID NO: 45) |

**Table 14.**

|           |                                 |
|-----------|---------------------------------|
| Gel No. 1 | VEGF + DMSO - 48hr              |
| Gel No. 2 | Compound 1 + VEGF + DMSO - 48hr |
| Gel No. 3 | VEGF + DMSO - 48hr              |

**Table 15.**

| <b>Spot #1202</b>                | <b>Run #1</b> | <b>Run #2</b> |
|----------------------------------|---------------|---------------|
| <b>Sample</b>                    |               |               |
| baseline                         | 126           | 22.5          |
| VEGF at 24h                      | 437           | 192.4         |
| VEGF at 48h                      | 812           | 540           |
| VEGF and compound 1 (1uM) at 24h | 270           | 484.7         |
| VEGF and compound 1 (1uM) at 48h | 869           | 158           |

Table 16.

| <u>SSP</u> | <u>Well</u> | <u>MALDI Mass Mapping result</u>   | <u>MS-Fit MOWSE Score</u> | <u>Sequence Coverage</u> |
|------------|-------------|------------------------------------|---------------------------|--------------------------|
| 1202       | A6          | Interstitial Collagenase Precursor | 3.64E+07                  | 31%                      |

Table 17.

| <u>SSP</u> | <u>Well</u> | <u>Confirmed Peptide</u>       | <u>File Name</u>      | <u>MS/MS result</u>  | <u>MASCOT Score</u> |
|------------|-------------|--------------------------------|-----------------------|--|---------------------|
| 1202       | A6          | DIYSSFGFPR<br>(SEQ ID NO: 46)  | spotA6-1188.wiff      | MM01_HUMAN, Interstitial Collagenase Precursor P03956<br>53973/6.4 | 34                  |
| 1202       | A6          | DGFFYFFHGTR<br>(SEQ ID NO: 47) | spotA6prod1393-2.wiff | MM01_HUMAN, Interstitial Collagenase Precursor P03956<br>53973/6.4 | 22                  |

**Table 18.**

| HUVEC SAMPLE <sup>1</sup>  | Average pro-MMP1 (ng/ml) | Standard Deviation |
|----------------------------|--------------------------|--------------------|
| VEGF 10 min                | 4.66                     | 0.3079             |
| DMSO 10 min                | 4.64                     | 0.1003             |
| compound 1 @ 10 nM 10 min  | 5.41                     | 0.1224             |
| Compound 1 @ 100 nM 10 min | 5.78                     | 0.3158             |
| Compound 1 @ 1 uM 10 min   | 5.04                     | 0.331              |
| VEGF 8 hr                  | 16.47                    | 1.0048             |
| DMSO 8 hr                  | 17.63                    | 1.2563             |
| Compound 1 @ 10 nM 8 hr    | 14.93                    | 1.1245             |
| Compound 1 @ 100 nM 8 hr   | 12.75                    | 0.6686             |
| Compound 1 @ 1 uM 8 hr     | 14.48                    | 1.0551             |
| VEGF 24 hr                 | 45.71                    | 3.06               |
| DMSO 24 hr                 | 79.94                    | 4.50               |
| Compound 1 @ 10 nM 24 hr   | 70.21                    | 4.82               |
| Compound 1 @ 100 nM 24 hr  | 50.26                    | 1.24               |
| Compound 1 @ 1 uM 24 hr    | 50.42                    | 2.42               |
| VEGF 48 hr                 | 244.74                   | 3.91               |
| DMSO 48 hr                 | 234.72                   | 10.85              |
| Compound 1 @ 10 nM 48 hr   | 135.35                   | 1.04               |
| Compound 1 @ 100 nM 48 hr  | 128.75                   | 11.05              |
| Compound 1 @ 1 uM 48 hr    | 103.09                   | 3.60               |

<sup>1</sup>Time points indicated (10 min, 8h, 24h, 48h) refer to the period of time post-VEGF treatment after which samples were isolated.



Table 19.

|                          | Pro-MMP1 (ng/ml) | FC vs d1 Pre <sup>1</sup> | % Change vs d1 Pre |
|--------------------------|------------------|---------------------------|--------------------|
| Pt 3 d1 Pre <sup>2</sup> | 0.3115           |                           |                    |
| d1 24 hr                 | 0.2837           | -1.097990835              | -8.924558587       |
| d13 Pre                  | 0.6756           | 2.168860353               | 116.8860353        |
| d13 12 hr                | 0.6235           | 2.001605136               | 100.1605136        |
| d13 24 hr                | 0.4035           | 1.295345104               | 29.53451043        |
| Pt 4 d1 Pre              | 0.5214           |                           |                    |
| d1 24 hr                 | 0.8938           | 2.869341894               | 71.42309168        |
| d13 Pre                  | 0.6246           | 2.005136437               | 19.79286536        |
| d13 12 hr                | 0.4579           | 1.469983949               | -12.17874952       |
| d13 24 hr                | 0.4514           | 1.449117175               | -13.42539317       |
| Pt 5 d1 Pre              | 0.5739           |                           |                    |
| d1 24 hr                 | 0.323            | 1.036918138               | -43.71841784       |
| d13 Pre                  | 0.7269           | 2.333547352               | 26.65969681        |
| d13 12 hr                | 0.6874           | 2.206741573               | 19.77696463        |
| d13 24 hr                | 0.4171           | 1.339004815               | -27.32183307       |
| Pt 6 d1 Pre              | 0.2969           |                           |                    |
| d1 24 hr                 | 0.6818           | 2.188764045               | 129.6396093        |
| d13 Pre                  | 0.7597           | 2.438844302               | 155.8773998        |
| d13 12 hr                | 0.7992           | 2.56565008                | 169.1815426        |
| d13 24 hr                | 1.066            | 3.422150883               | 259.043449         |
| Pt 7 d1 Pre              | 0.5743           |                           |                    |
| d1 24 hr                 | 0.7334           | 2.354414125               | 27.70329096        |
| d13 Pre                  | 0.7374           | 2.367255217               | 28.39979105        |
| d13 12 hr                | 0.5154           | 1.654574639               | -10.25596378       |
| d13 24 hr                | 0.7203           | 2.312359551               | 25.42225318        |
| Pt 8 d1 Pre              | 0.2879           |                           |                    |
| d1 24 hr                 | 0.3664           | 1.176243981               | 27.26641195        |
| d13 Pre                  | 1.7166           | 5.510754414               | 496.2486975        |
| d13 12 hr                | 1.1071           | 3.554093098               | 284.5432442        |
| d13 24 hr                | 0.8494           | 2.726805778               | 195.0329976        |
| Pt 9 d1 Pre              | 0.7786           |                           |                    |
| d1 24 hr                 | 0.4816           | 1.546067416               | -38.14538916       |
| d13 Pre                  | 0.4931           | 1.582985554               | -36.66837914       |
| d13 12 hr                | 1.047            | 3.361155698               | 34.47212946        |
| d13 24 hr                | 2.6022           | 8.353772071               | 234.2152582        |
| Pt 10 d1 Pre             | 0.3613           |                           |                    |
| d1 24 hr                 | 0.2396           | -1.300083472              | -33.68391918       |
| d13 Pre                  | 1.2937           | 4.153130016               | 258.0680875        |
| d13 12 hr                | 1.4224           | 4.566292135               | 293.6894547        |
| d13 24 hr                | 1.0684           | 3.429855538               | 195.7099363        |

**Table 19 cont.**

|                     |        |             |              |
|---------------------|--------|-------------|--------------|
| <b>Pt 11 d1 Pre</b> | 0.299  |             |              |
| <b>d1 24 hr</b>     | 0.2866 | -1.08688067 | -4.147157191 |
| <b>d13 Pre</b>      | 0.6931 | 2.225040128 | 131.8060201  |
| <b>d13 12 hr</b>    | 0.4496 | 1.443338684 | 50.36789298  |
| <b>d13 24 hr</b>    | 1.1685 | 3.751203852 | 290.8026756  |
| <b>Pt 12 d1 Pre</b> | 0.8587 |             |              |
| <b>d1 24 hr</b>     | 0.5418 | 1.739325843 | -36.90462327 |
| <b>d13 Pre</b>      | 2.1689 | 6.962760835 | 152.5794806  |
| <b>d13 12 hr</b>    | 2.1494 | 6.900160514 | 150.308606   |
| <b>d13 24 hr</b>    | 5.9226 | 19.01316212 | 589.7170141  |

<sup>1</sup> Fold change of pro-MMP1 levels are indicated by “FC vs d1 pre”. These levels were calculated by dividing the levels of pro-MMP1 after drug treatment by the MMP1 levels present before drug treatment (d1 pre).

<sup>2</sup> Patient number is indicated (Pt), time point of sampling is indicated pre-treatment (d1 pre), 24 hours post first treatment (d1 24h), after 13 days of treatment (d13 pre), after 13 days and 12 hours post-treatment (d13 12h), and 13 days and 24hours of treatment (d13 24h).

Table 20.

|                     |                     |                    |                    |                    |                    |                    |                   |                   |                   |                   |                   |                   |                   |                     |                     |
|---------------------|---------------------|--------------------|--------------------|--------------------|--------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|---------------------|---------------------|
| 5000 ng/mL Bio-migG | 4000 ng/mL Bio-migG | BLANK              | AR                 | BDNF               | FGF-6              | Flt3Lig            | G-CSF             | HCC4              | I-309             | IL-1 $\alpha$     | IL-1 $\beta$      | IL-1 $\alpha$ R1  | 0 ng/mL Bio-migG  | 3000 ng/mL Bio-migG | 2000 ng/mL Bio-migG |
| 5000 ng/mL Bio-migG | 4000 ng/mL Bio-migG | BLANK              | AR                 | BDNF               | FGF-6              | Flt3Lig            | G-CSF             | HCC4              | I-309             | IL-1 $\alpha$     | IL-1 $\beta$      | IL-1 $\alpha$ R1  | 0 ng/mL Bio-migG  | 3000 ng/mL Bio-migG | 2000 ng/mL Bio-migG |
| 5000 ng/mL Bio-migG | 4000 ng/mL Bio-migG | BLANK              | AR                 | BDNF               | FGF-6              | Flt3Lig            | G-CSF             | HCC4              | I-309             | IL-1 $\alpha$     | IL-1 $\beta$      | IL-1 $\alpha$ R1  | 0 ng/mL Bio-migG  | 3000 ng/mL Bio-migG | 2000 ng/mL Bio-migG |
| 5000 ng/mL Bio-migG | 4000 ng/mL Bio-migG | BLANK              | AR                 | BDNF               | FGF-6              | Flt3Lig            | G-CSF             | HCC4              | I-309             | IL-1 $\alpha$     | IL-1 $\beta$      | IL-1 $\alpha$ R1  | 0 ng/mL Bio-migG  | 3000 ng/mL Bio-migG | 2000 ng/mL Bio-migG |
| 1000 ng/mL Bio-migG | 800 ng/mL Bio-migG  | 600 ng/mL Bio-migG | 400 ng/mL Bio-migG | 300 ng/mL Bio-migG | 200 ng/mL Bio-migG | 100 ng/mL Bio-migG | 80 ng/mL Bio-migG | 60 ng/mL Bio-migG | 50 ng/mL Bio-migG | 40 ng/mL Bio-migG | 30 ng/mL Bio-migG | 20 ng/mL Bio-migG | 10 ng/mL Bio-migG | 5 ng/mL Bio-migG    | Blank               |
| 1000 ng/mL Bio-migG | 800 ng/mL Bio-migG  | 600 ng/mL Bio-migG | 400 ng/mL Bio-migG | 300 ng/mL Bio-migG | 200 ng/mL Bio-migG | 100 ng/mL Bio-migG | 80 ng/mL Bio-migG | 60 ng/mL Bio-migG | 50 ng/mL Bio-migG | 40 ng/mL Bio-migG | 30 ng/mL Bio-migG | 20 ng/mL Bio-migG | 10 ng/mL Bio-migG | 5 ng/mL Bio-migG    | Blank               |
| 1000 ng/mL Bio-migG | 800 ng/mL Bio-migG  | 600 ng/mL Bio-migG | 400 ng/mL Bio-migG | 300 ng/mL Bio-migG | 200 ng/mL Bio-migG | 100 ng/mL Bio-migG | 80 ng/mL Bio-migG | 60 ng/mL Bio-migG | 50 ng/mL Bio-migG | 40 ng/mL Bio-migG | 30 ng/mL Bio-migG | 20 ng/mL Bio-migG | 10 ng/mL Bio-migG | 5 ng/mL Bio-migG    | Blank               |
| 1000 ng/mL Bio-migG | 800 ng/mL Bio-migG  | 600 ng/mL Bio-migG | 400 ng/mL Bio-migG | 300 ng/mL Bio-migG | 200 ng/mL Bio-migG | 100 ng/mL Bio-migG | 80 ng/mL Bio-migG | 60 ng/mL Bio-migG | 50 ng/mL Bio-migG | 40 ng/mL Bio-migG | 30 ng/mL Bio-migG | 20 ng/mL Bio-migG | 10 ng/mL Bio-migG | 5 ng/mL Bio-migG    | Blank               |
| GCP-2               | NT3                 | NT4                | PARC               | Rantes             | SCF                | SDF-1 $\alpha$     | sgp130            | TARC              | TGF- $\beta$ 1    | TNF- $\alpha$     | TNF- $\beta$      | TNF-R1            | TNF-RII           | VEGF                | Blank               |
| GCP-2               | NT3                 | NT4                | PARC               | Rantes             | SCF                | SDF-1 $\alpha$     | sgp130            | TARC              | TGF- $\beta$ 1    | TNF- $\alpha$     | TNF- $\beta$      | TNF-R1            | TNF-RII           | VEGF                | Blank               |
| GCP-2               | NT3                 | NT4                | PARC               | Rantes             | SCF                | SDF-1 $\alpha$     | sgp130            | TARC              | TGF- $\beta$ 1    | TNF- $\alpha$     | TNF- $\beta$      | TNF-R1            | TNF-RII           | VEGF                | Blank               |
| GCP-2               | NT3                 | NT4                | PARC               | Rantes             | SCF                | SDF-1 $\alpha$     | sgp130            | TARC              | TGF- $\beta$ 1    | TNF- $\alpha$     | TNF- $\beta$      | TNF-R1            | TNF-RII           | VEGF                | Blank               |
| Blank               | IL-2                | IL-6 $\alpha$ R    | IL-11              | IL-12 p70          | IL-16              | IL-17              | IP-10             | LIF               | MCP-1             | M-CSF             | MDC               | MIG               | MIP-1 $\beta$     | MIP-1 $\delta$      | NAP-2               |
| Blank               | IL-2                | IL-6 $\alpha$ R    | IL-11              | IL-12 p70          | IL-16              | IL-17              | IP-10             | LIF               | MCP-1             | M-CSF             | MDC               | MIG               | MIP-1 $\beta$     | MIP-1 $\delta$      | NAP-2               |
| Blank               | IL-2                | IL-6 $\alpha$ R    | IL-11              | IL-12 p70          | IL-16              | IL-17              | IP-10             | LIF               | MCP-1             | M-CSF             | MDC               | MIG               | MIP-1 $\beta$     | MIP-1 $\delta$      | NAP-2               |
| Blank               | IL-2                | IL-6 $\alpha$ R    | IL-11              | IL-12 p70          | IL-16              | IL-17              | IP-10             | LIF               | MCP-1             | M-CSF             | MDC               | MIG               | MIP-1 $\beta$     | MIP-1 $\delta$      | NAP-2               |

**Table 21.**

| Patient         | 1, 2, 3   | Patient      | 1, 2, 3   |
|-----------------|-----------|--------------|-----------|
| • ENA-78        | (-) ↓ ↓   | TNFR1        | ↑ ↑ (-)   |
| • MPIF-1        | (-) (-) ↓ | VEGF         | ↑ ↑ (-)   |
| • GCP-2         | ↑ (-) (-) | Flt3L        | ↑ ↑ ↑     |
| • Amphireg      | ↑ (-) (-) | PLGF         | ↑ ↑ (-)   |
| • IL-1 $\alpha$ | ↑ ↑ (-)   | IL6          | ↑ ↑ (-)   |
| • IL-1 $\beta$  | ↑ ↑ (-)   | MCP-1        | ↑ ↑ (-)   |
| • IL-2          | ↑ ↑ (-)   | TNF $\alpha$ | ↑ ↑ (-)   |
| • MIG           | (-) ↓ (-) | TARC         | ↑ (-) (-) |
| • NT4           | ↑ (-) ↑   | MMP7         | ↑ ↑ ↓     |
| • GCP-2         | ↑ ↑ (-)   | MMP9         | (-) (-) ↑ |
| • IGFBP-1       | ↑ ↑ ↑     | leptin       | (-) ↑ (-) |
| • GRO- $\beta$  | ↑ (-) ↑   |              |           |

Table 22.

|               | Patient 1 |         | Patient 2 |         | Patient 3 |         |
|---------------|-----------|---------|-----------|---------|-----------|---------|
|               | ELISA     | Ab Chip | ELISA     | Ab Chip | ELISA     | Ab Chip |
| <b>VEGF</b>   | 32        | 2.7     | 72        | 4.3     | 3         | 1.8     |
| <b>PLGF</b>   | 13        | 4.6     | 25.1      | 21.7    | 5.3       | 1.6     |
| <b>IL-6</b>   | 29        | 2.9     | 11.6      | 3.7     | 0.9       | 0.99    |
| <b>IL-8</b>   | 2         | 1.5     | 2.7       | 1.8     | 0.77      | 1.7     |
| <b>FLT3 L</b> | 10.3      | 13.9    | 6.7       | 7.7     | 2.6       | 6.2     |
| <b>MCP-1</b>  | 2.2       | 2.5     | 1.93      | 2       | 1.0       | 1.4     |

We claim:

1. A method for determining whether a test compound inhibits tyrosine kinase activity in a mammal, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcript measured in (c), compared to the level of protein and/or mRNA transcript measured in step (a) indicates that the test compound is an inhibitor of tyrosine kinase in the mammal.

2. A method for determining whether a test compound inhibits tyrosine kinase activity in a mammal, comprising:

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the compound is an inhibitor of tyrosine kinase in the mammal.

3. A method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;



(b), exposing the mammal to the test compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA measured in (c), compared to the level of protein and/or mRNA in step (a) indicates that the mammal has been exposed to a test compound that inhibits tyrosine kinase activity.

4. A method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity, comprising

(a) exposing the mammal to the test compound; and

(b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-

cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the mammal has been exposed to a test compound that is an inhibitor of tyrosine kinase.

5. A method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity, comprising:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-

binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b), exposing the mammal to the compound; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that the mammal is responding to the compound that inhibits tyrosine kinase activity.

6. A method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity, comprising:

(a) exposing the mammal to the compound; and

(b) following the exposing step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo

sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said compound, indicates that the mammal is responding to the compound that inhibits tyrosine kinase.

7. A method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase, wherein the method for identifying the mammal comprises:

(a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb

gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) exposing the mammal to at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase; and

(c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a),

wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase.

8. A method for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase, wherein the method for testing or predicting comprises:

(a) measuring in a mammal with cancer the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic

transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(b) measuring in the same type of mammal without cancer, the level of at least one of the same proteins and/or mRNA transcripts measured in step (a);

(c) comparing levels of said proteins and/or mRNA transcripts measured in (a) and (b);

wherein a difference in the level of said protein and/or mRNA in the mammal with cancer as measured in step (a), compared to the level of said protein and/or mRNA in the mammal without cancer as measured in step (b), indicates that the mammal will respond therapeutically to at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase.

9. The method of any one of claims 1-8, wherein the mammal is a human, rat, mouse, dog, rabbit, pig, sheep, cow, horse, cat, primate or monkey.

10. The method of any one of claims 1-8, wherein the method is an in vitro method, and wherein the protein and/or mRNA is measured in at least one mammalian biological tissue from the mammal.

11. The method of claim 10, wherein the biological tissue comprises a biological fluid that is selected from the group consisting of whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine and saliva.

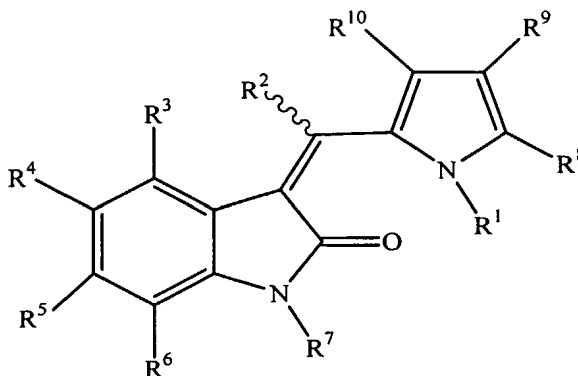
12. The method of claim 10, wherein the tissue is selected from the group consisting of buccal mucosa tissue, skin, hair follicles, tumor tissue and bone marrow.

13. The method of any one of claims 1-8, wherein the mammal has cancer.

14. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is an indolinone compound.

15. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is:

a pyrrole substituted 2-indolinone having the formula:



wherein:

$R^1$ ,  $R^2$  and  $R^7$  are hydrogen;

$R^3$ ,  $R^4$ ,  $R^5$ , and  $R^6$  are independently selected from the group consisting of hydrogen, hydroxy, halo, unsubstituted lower alkyl, lower alkyl substituted with a carboxylic acid, unsubstituted lower alkoxy, carboxylic acid, unsubstituted aryl, aryl substituted with one or more unsubstituted lower alkyl alkoxy, and morpholino;

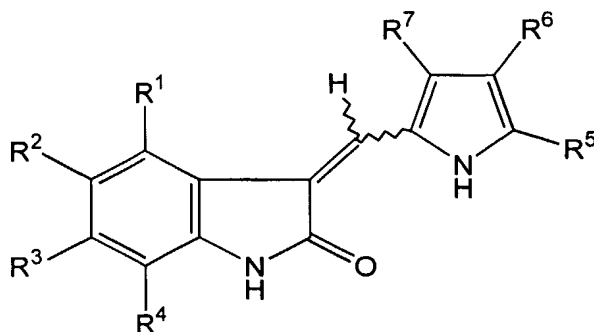
$R^8$  is unsubstituted lower alkyl;

$R^9$  is  $-(CH_2)(CH_2)C(=O)OH$ ; and

$R^{10}$  is unsubstituted lower alkyl;

or a pharmaceutically acceptable salt thereof; or

a compound having the formula:



wherein:

$R^1$  is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy,  $-(CO)R^{15}$ ,  $-NR^{13}R^{14}$ ,  $-(CH_2)_rR^{16}$  and  $-C(O)NR^8R^9$ ;

$R^2$  is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano,  $-NR^{13}R^{14}$ ,  $-NR^{13}C(O)R^{14}$ ,  $-C(O)R^{15}$ , aryl, heteroaryl, and  $-S(O)_2NR^{13}R^{14}$ ;

$R^3$  is selected from the group consisting of hydrogen, halogen, alkyl, trihalomethyl, hydroxy, alkoxy,  $-(CO)R^{15}$ ,  $-NR^{13}R^{14}$ , aryl, heteroaryl,  $-NR^{13}S(O)_2R^{14}$ ,  $-S(O)_2NR^{13}R^{14}$ ,  $-NR^{13}C(O)R^{14}$ ,  $-NR^{13}C(O)OR^{14}$  and  $-SO_2R^{20}$  (wherein  $R^{20}$  is alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl);

$R^4$  is selected from the group consisting of hydrogen, halogen, alkyl, hydroxy, alkoxy and  $-NR^{13}R^{14}$ ;

$R^5$  is selected from the group consisting of hydrogen, alkyl and  $-C(O)R^{10}$ ;

$R^6$  is selected from the group consisting of hydrogen, alkyl and  $-C(O)R^{10}$ ;

$R^7$  is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl,  $-C(O)R^{17}$  and  $-C(O)R^{10}$ ; or

$R^6$  and  $R^7$  may combine to form a group selected from the group consisting of  $-(CH_2)_4-$ ,  $-(CH_2)_5-$  and  $-(CH_2)_6-$ ;

with the proviso that at least one of  $R^5$ ,  $R^6$  or  $R^7$  must be  $-C(O)R^{10}$ ;

$R^8$  and  $R^9$  are independently selected from the group consisting of hydrogen, alkyl and aryl;

$R^{10}$  is selected from the group consisting of hydroxy, alkoxy, aryloxy,  $-N(R^{11})(CH_2)_nR^{12}$ , and  $-NR^{13}R^{14}$ ;



$R^{11}$  is selected from the group consisting of hydrogen and alkyl;

$R^{12}$  is selected from the group consisting of  $-NR^{13}R^{14}$ , hydroxy,  $-C(O)R^{15}$ , aryl, heteroaryl,  $-N^+(O^-)R^{13}R^{14}$ ,  $-N(OH)R^{13}$ , and  $-NHC(O)R^a$  (wherein  $R^a$  is unsubstituted alkyl, haloalkyl, or aralkyl);

$R^{13}$  and  $R^{14}$  are independently selected from the group consisting of hydrogen, alkyl, lower alkyl substituted with hydroxyalkylamino, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

$R^{13}$  and  $R^{14}$  may combine to form a heterocyclo group;

$R^{15}$  is selected from the group consisting of hydrogen, hydroxy, alkoxy and aryloxy;

$R^{16}$  is selected from the group consisting of hydroxy,  $-C(O)R^{15}$ ,  $-NR^{13}R^{14}$  and  $-C(O)NR^{13}R^{14}$ ;

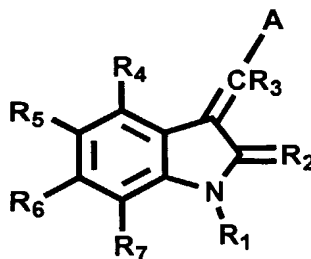
$R^{17}$  is selected from the group consisting of alkyl, cycloalkyl, aryl and heteroaryl;

$R^{20}$  is alkyl, aryl, aralkyl or heteroaryl; and

n and r are independently 1, 2, 3, or 4;

or a pharmaceutically acceptable salt thereof; or

a compound having the formula:



wherein:

$R_1$  is H;

$R_2$  is O or S;

$R_3$  is hydrogen;

$R_4$ ,  $R_5$ ,  $R_6$ , and  $R_7$  are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl,  $S(O)R$ ,  $SO_2NRR'$ ,  $SO_3R$ ,  $SR$ ,  $NO_2$ ,  $NRR'$ ,  $OH$ ,  $CN$ ,  $C(O)R$ ,  $OC(O)R$ ,  $NHC(O)R$ ,  $(CH_2)_nCO_2R$ , and  $CONRR'$ ;

A is a five membered heteroaryl ring selected from the group consisting of thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-

oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, optionally substituted at one or more positions with alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO<sub>2</sub>NRR', SO<sub>3</sub>R, SR, NO<sub>2</sub>, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, (CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>R or CONRR';

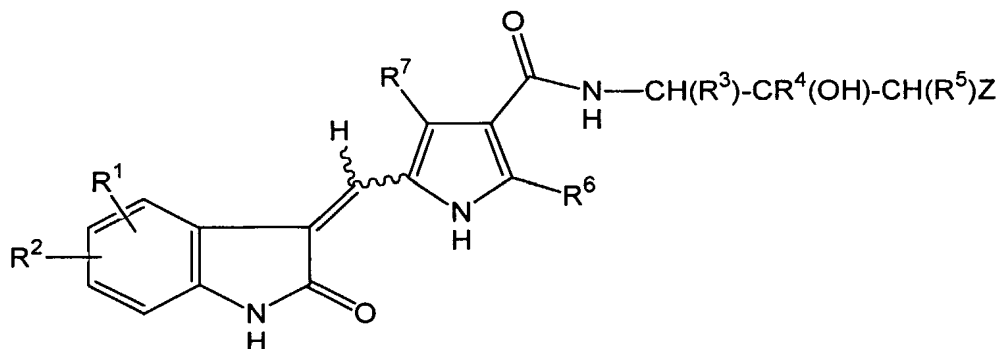
n is 0-3;

R is H, alkyl or aryl; and

R' is H, alkyl or aryl;

or a pharmaceutically acceptable salt thereof; or

a compound having the formula:



wherein:

R<sup>1</sup> is selected from the group consisting of hydrogen, halo, alkyl, haloalkoxy, cycloalkyl, heteroalicyclic, hydroxy, alkoxy, -C(O)R<sup>8</sup>, -NR<sup>9</sup>R<sup>10</sup> and -C(O)NR<sup>12</sup>R<sup>13</sup>;

R<sup>2</sup> is selected from the group consisting of hydrogen, halo, alkyl, trihalomethyl, hydroxy, alkoxy, cyano, -NR<sup>9</sup>R<sup>10</sup>, -NR<sup>9</sup>C(O)R<sup>10</sup>, -C(O)R<sup>8</sup>, -S(O)<sub>2</sub>NR<sup>9</sup>R<sup>10</sup> and -SO<sub>2</sub>R<sup>14</sup> (wherein R<sup>14</sup> is alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl);

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently hydrogen or alkyl;

Z is aryl, heteroaryl, heterocycle, or -NR<sup>15</sup>R<sup>16</sup> wherein R<sup>15</sup> and R<sup>16</sup> are independently hydrogen or alkyl; or R<sup>15</sup> and R<sup>16</sup> together with the nitrogen atom to which they are attached from a heterocycloamino group;

R<sup>6</sup> is selected from the group consisting of hydrogen or alkyl;

R<sup>7</sup> is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and -C(O)R<sup>17</sup> as defined below;

R<sup>8</sup> is selected from the group consisting of hydroxy, alkoxy and aryloxy;

$R^9$  and  $R^{10}$  are independently selected from the group consisting of hydrogen, alkyl, cyanoalkyl, cycloalkyl, aryl and heteroaryl; or

$R^9$  and  $R^{10}$  combine to form a heterocycloamino group;

$R^{12}$  and  $R^{13}$  are independently selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, and aryl; or  $R^{12}$  and  $R^{13}$  together with the nitrogen atom to which they are attached form a heterocycloamino;

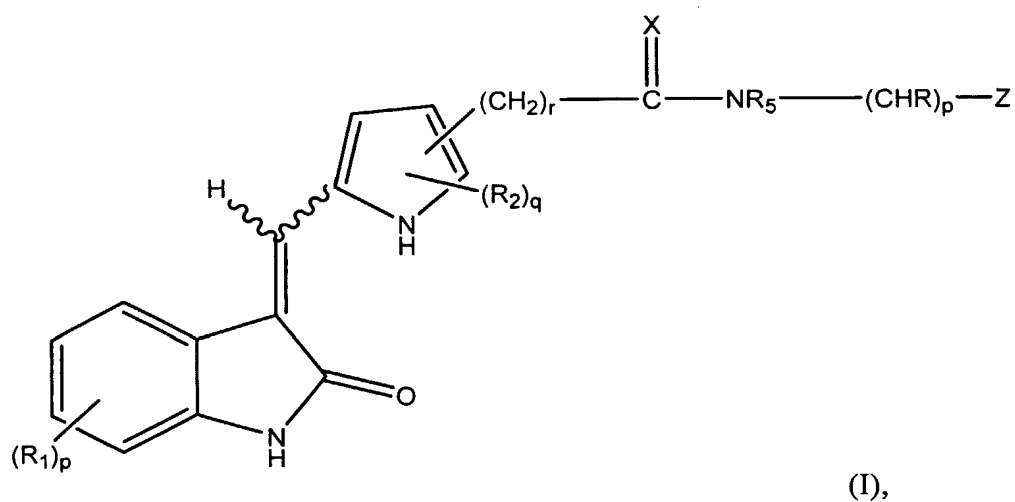
$R^{17}$  is selected from the group consisting of alkyl, cycloalkyl, aryl, hydroxy and heteroaryl;

or a pharmaceutically acceptable salt thereof.

16. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid (Compound A) or a pharmaceutically acceptable salt thereof.

17. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is 3-(3,5-dimethyl-1H-pyrrol-2-ylmethylene)-1,3-dihydro-indol-2-one (Compound B) or a pharmaceutically acceptable salt thereof.

18. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is a compound of Formula I:



wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each  $R_1$  is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy,  $-C(O)-R_8$ ,  $-NR_9R_{10}$ ,  $-NR_9C(O)-R_{12}$  and  $-C(O)NR_9R_{10}$ ;

each  $R_2$  is independently selected from the group consisting of alkyl, aryl, heteroaryl,  $-C(O)-R_8$ , and  $SO_2R''$ , where  $R''$  is alkyl, aryl, heteroaryl,  $NR_9N_{10}$  or alkoxy;

each  $R_5$  is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy,  $-C(O)-R_8$  and  $(CHR)_rR_{11}$ ;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

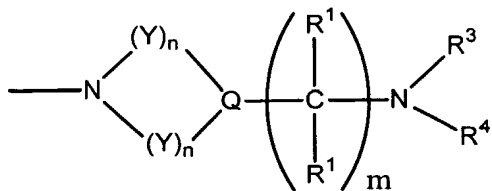
$R_8$  is selected from the group consisting of  $-OH$ , alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

$R_9$  and  $R_{10}$  are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or  $R_9$  and  $R_{10}$  together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

$R_{11}$  is selected from the group consisting of  $-OH$ , amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

$R_{12}$  is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH, O-alkyl, or  $-NR_3R_4$ , where  $R_3$  and  $R_4$  are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or  $R_3$  and  $R_4$  may combine with N to form a ring where the ring atoms are selected from the group consisting of  $CH_2$ , N, O and S or



wherein Y is independently  $CH_2$ , O, N or S,

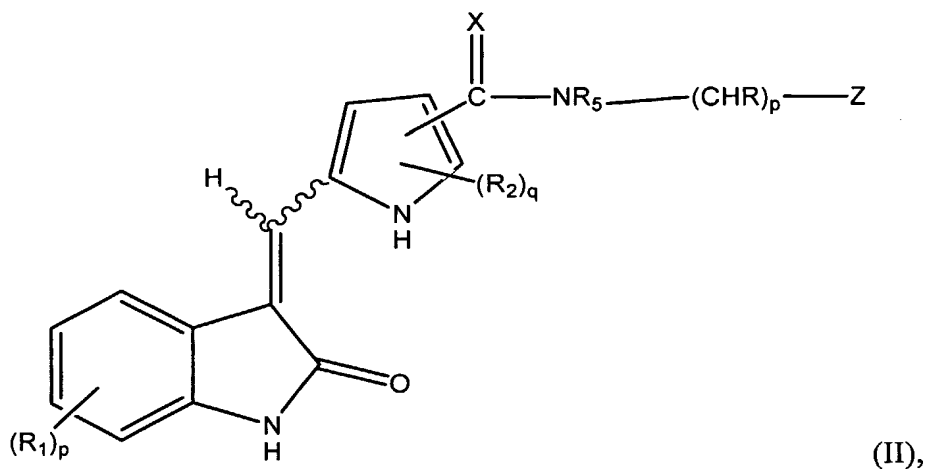
Q is C or N;

n is independently 0-4; and

m is 0-3;

or a pharmaceutically acceptable salt thereof.

19. The method of any one of claims 1-8, wherein the compound that inhibits tyrosine kinase activity is a compound of Formula II:



wherein:

R is independently H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclic and amino;

each  $R_1$  is independently selected from the group consisting of alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclic, hydroxy,  $-C(O)-R_8$ ,  $-NR_9R_{10}$ ,  $-NR_9C(O)-R_{12}$  and  $-C(O)NR_9R_{10}$ ;

each  $R_2$  is independently selected from the group consisting of alkyl, aryl, heteroaryl,  $-C(O)-R_8$ , and  $SO_2R''$ , where  $R''$  is alkyl, aryl, heteroaryl,  $NR_9N_{10}$  or alkoxy;

each  $R_5$  is independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclic, hydroxy,  $-C(O)-R_8$  and  $(CHR)_rR_{11}$ ;

X is O or S;

p is 0-3;

q is 0-2;

r is 0-3;

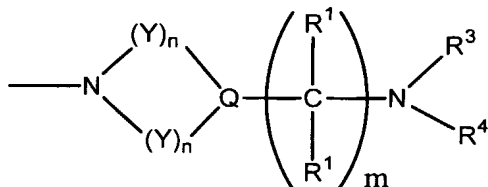
$R_8$  is selected from the group consisting of  $-OH$ , alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

$R_9$  and  $R_{10}$  are independently selected from the group consisting of H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl and heterocyclic, or  $R_9$  and  $R_{10}$  together with N may form a ring, where the ring atoms are selected from the group consisting of C, N, O and S;

$R_{11}$  is selected from the group consisting of  $-OH$ , amino, monosubstituted amino, disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic

$R_{12}$  is selected from the group consisting of alkyl, aryl, heteroaryl, alkoxy, cycloalkyl and heterocyclic;

Z is OH, O-alkyl, or  $-NR_3R_4$ , where  $R_3$  and  $R_4$  are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclic, or  $R_3$  and  $R_4$  may combine with N to form a ring where the ring atoms are selected from the group consisting of  $CH_2$ , N, O and S or



wherein Y is independently  $CH_2$ , O, N or S,

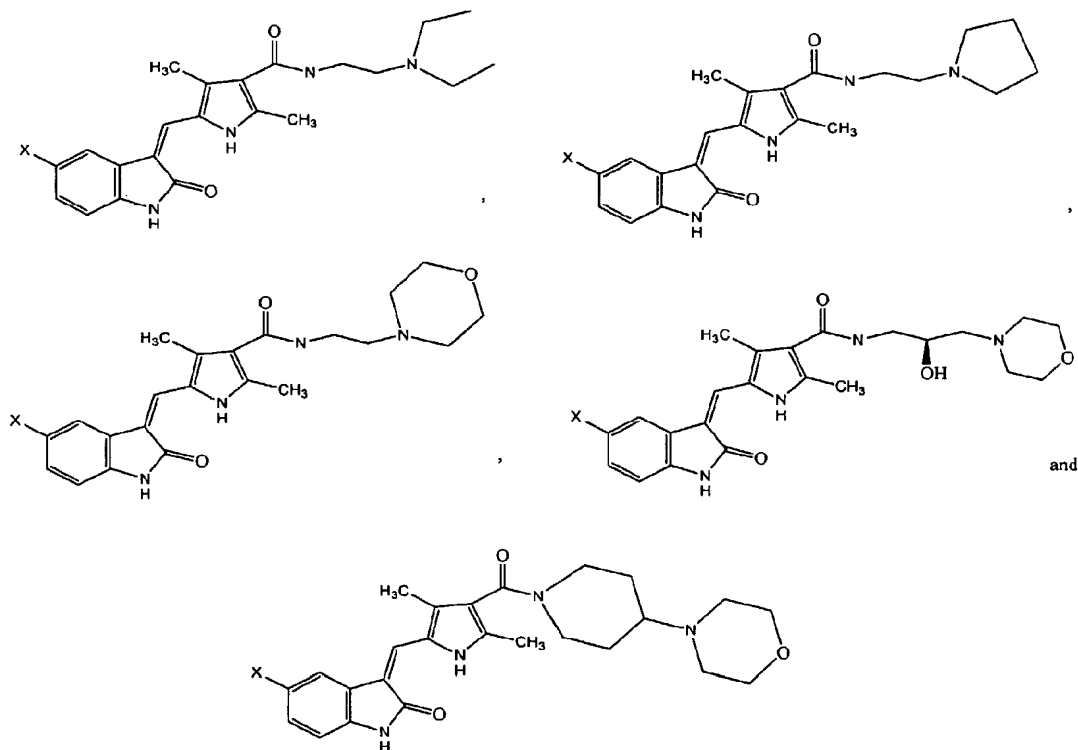
Q is C or N;

n is independently 0-4; and

m is 0-3;

or a pharmaceutically acceptable salt thereof.

20. The method of claim 18, wherein the compound that inhibits tyrosine kinase activity is selected from the group consisting of:



wherein X is F, Cl, I or Br;

or a pharmaceutically acceptable salt thereof.

21. The method of claim 18, wherein the compound of Formula I is 5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (Compound 1).

22. A kit comprising:

(a) antibody and/or nucleic acid for detecting the presence of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein

A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; and

(b) instructions for determining whether or not a mammal will respond therapeutically to a method of treating cancer comprising administering a compound that inhibits tyrosine kinase activity.

23. A kit of claim 22, wherein said instructions comprise the steps of:

(i) measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal



phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, NT4, GCP-2, IGFBP-1, GRO- $\beta$ , TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF $\alpha$ , TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

(ii) exposing the mammal to a compound that inhibits tyrosine kinase activity; and

(iii) following the exposing step of (ii), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts for such proteins measured in step (i);

wherein a difference in the level of said proteins and/or mRNA transcripts measured in (iii), compared to the level of proteins and or mRNA transcripts measured in step (i) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering the compound that inhibits tyrosine kinase activity.

24. A method for testing or predicting whether a mammal will experience an adverse event in response to a method of treating cancer comprising administering a tyrosine kinase inhibitor, wherein the method for testing or predicting comprises:

(a) measuring in the mammal the level of IL-6 or C-reactive protein (CRP) protein and/or mRNA transcript for such protein and/or gene before administering the tyrosine kinase inhibitor;

(b) measuring in the mammal the level of IL-6 or CRP protein and/or mRNA transcript for such protein and/or gene after administering the tyrosine kinase inhibitor;

(c) comparing levels of said IL-6 or CRP protein and/or mRNA transcript measured in (a) and (b);

wherein a level of two-fold or greater of said protein and/or mRNA transcript as measured in step (b), compared to the level of said protein and/or mRNA transcript as measured in step (a), indicates that the mammal will experience fatigue in response to the method of treating cancer comprising administering the tyrosine kinase inhibitor.

25. The method of claim 24, wherein the tyrosine kinase inhibitor is a compound of Formula I or salt thereof.

26. The method of claim 25, wherein the compound of Formula I or salt thereof is 5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (Compound 1) or salt thereof.

27. A method of claim 24, wherein the adverse event is debilitating fatigue.

28. The method of claim 24, wherein the method is an in vitro method, and wherein the protein and/or mRNA is measured in at least one biological tissue from the mammal.

29. The method of claim 24, wherein the biological tissue comprises a biological fluid that is selected from the group consisting of whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine and saliva.

30. The method of claim 24, wherein the tissue is selected from the group consisting of buccal mucosa tissue, skin, hair follicles, tumor tissue and bone marrow.



Figure 2.

|                                |       |      |        | DIFFERENCE VALUES (percent change)    |                                       |                                       |  |                                       |  |   |  |  |  |
|--------------------------------|-------|------|--------|---------------------------------------|---------------------------------------|---------------------------------------|--|---------------------------------------|--|---|--|--|--|
|                                |       |      |        | pt 1 pre v 4 hr post<br>d.1 200 mg/m2 | pt 8 pre v 4 hr post<br>d.1 200 mg/m2 | pt 9 pre v 4 hr post<br>d.1 200 mg/m2 | pt 10 pre v 4 hr post<br>d.1 200 mg/m2 | pt 12 pre v 4hr post<br>d.1 200 mg/m2 | pt 1 d1 pre vs 4 hr post<br>800 vs 200 mg/m2 | pt 1 pre-dose d 28vs<br>d1 pre-dose 200 mg/m2 |  |  |  |
| Cmax (ug/ml)                   |       |      |        | 16.4                                  | 2.5                                   | 7.4                                   | 15.8                                   | 15.1                                  | 27   | 8.9   |  |  |  |
| AUC <sub>0-24</sub> (ug hr/ml) |       |      |        | 94.7                                  | 36.2                                  | 50.2                                  | 148.4                                  | 102.4                                 | 175.3  | 57.2  |  |  |  |
| Exposure>2.3 ug/ml (hrs)       |       |      |        | 13.2                                  | 2.2                                   | 6.6                                   | 19.8                                   | 12.5                                  | 20.6   | 9.7   |  |  |  |
| CLASS                          | spot# | pl   | MW     |                                       |                                       |                                       |  |                                       |  |   |  |  |  |
| 1                              | 5     | 5.79 | 140776 | 104                                   | 12                                    | 79                                    | 16                                     | 46                                    | 204  | 0   |  |  |  |

Difference= (1- spot% sample X/ spot% sample ref)/(-100)

Duplicate gels were run for each (pre and post) sample. Averaged values were used for the calculations.

- is up in post versus pre
- + is down in post versus pre

IEF with pH 4-8 ampholines. Fifty ng of IEF standard tropomyosin added to each sample before loading.

SDS slb gels are 10%

Figure 3.

| SPOT # | w/SU006668 | MS-MS Identification                      | potential role          |
|--------|------------|---|-------------------------|
| 5      | ↓          | ITIH4 (inter-alpha globulin inhibitor H4) | acute phase IL6 induced |

Figure 4A.

|                         | Patient #   | 017              | 019              | 022              | 027              | 028              |
|-------------------------|-------------|------------------|------------------|------------------|------------------|------------------|
| Gene Name               | Accession # | Taq/Affy<br>F.C. | Taq/Affy<br>F.C. | Taq/Affy<br>F.C. | Taq/Affy<br>F.C. | Taq/Affy<br>F.C. |
| VEGF                    | AF022375    | 3.51/ND          | 1.49/0.8         | 1.68/ND          | 2.91/0.5         | 0.27/0.198       |
| MAPK<br>Kinase3         | L36719      | 1.14/0.65        | 0.26/2.56        | 0.75/0.67        | 0.54/1.96        | 0.21/0.39        |
| PECAM                   | L34657      | 0.72/ND          | 0.99/0.60        | 1.01/ND          | 0.75/0.92        | 0.22/0.23        |
| Hemoglobin<br>Epsilon 1 | A1349593    | ND/1.53          | ND/3.05          | ND/ND            | ND/3.06          | ND/2.9           |
| Vinculin                | M33308      | 32.19/1.96       | 1.43/0.75        | 1.71/1.21        | 1.84/0.62        | 8.24/3.72        |

<sup>1</sup>Normalized against 18S

F.C. = Fold Change

ND = Not detected

Table 4B.

| Patient # | Taqman/Affy<br>Fold Change | SU6668<br>Dose<br>(mg/m <sup>2</sup> ) | SU6668<br>Cmax<br>(µg/ml) | SU6668<br>AUC<br>(µg*hr/ml) | SU6668<br>Exposure<br>>2.3 µg/ml (hrs) | Tumor<br>Types |
|-----------|----------------------------|--|---------------------------|-----------------------------|--|----------------|
| 17        | 32.19/1.96                 | 200 BID                                | 11.5                      | 66.1                        | 11                                     | Colon/Rectal   |
| 27        | 1.84/0.62                  | 400 BID                                | 10.3                      | 71.2                        | 9.1                                    | Colon/Rectal   |
| 28        | 8.24/3.72                  | 400 BID                                | 13                        | 164.3                       | 21.3                                   | Prostate       |



Figure 6.

Defensin  $\alpha$  4  
CEA CAM 8  
BPI  
MMP-9  
Lipocalin 2  
S100 P  
Hypothetical protein FLJ13052  
Liver arginase  
CD24 antigen  
Defensin  $\alpha$  3  
Antileuko-protease  
Thrombospondin 1  
Lactoferrin

| SU5416 Arm |    |    |    |    |    |    |    |    |    |    |    |
|------------|----|----|----|----|----|----|----|----|----|----|----|
| PR         | PR | PR | PR | PR | PR | PD | PD | PD | PD | PD |    |
|            |    |    |    |    |    |    |    |    |    |    | NC |
|            |    | NC |    |    |    |    |    |    |    |    | NC |
|            |    | NC |    |    |    |    |    |    |    |    | NC |
|            |    | NC |    |    |    |    |    | NC |    |    | NC |
|            |    | NC |    |    |    |    |    | MI |    |    |    |
|            | NC |    |    |    |    |    |    |    |    |    | NC |
| NC         | NC | NC |    |    |    |    |    | D  |    |    |    |
|            |    | NC |    |    |    |    |    |    |    |    | NC |
|            |    | NC |    |    |    |    |    |    |    |    | NC |
| MI         |    |    | MI |    |    | NC |    |    |    |    |    |
|            |    | NC |    |    | NC |    |    | NC |    |    |    |
|            |    |    | MD |    | NC |    |    |    |    |    |    |
|            |    |    |    |    |    |    |    |    |    |    |    |

| Control Arm |    |    |    |    |    |    |    |    |    |    |    |
|-------------|----|----|----|----|----|----|----|----|----|----|----|
| CR          | PR | PR | PR | PR | PR | PD | PD | PD | PD | PD | PD |
| NC          | NC | NC | NC |    | NC |    |    |    |    |    | NC |
| NC          | NC | NC | NC |    | NC |    | NC |    | NC |    | NC |
| NC          | NC | NC | NC | NC | NC |    |    |    | NC |    | NC |
|             | D  | NC | D  | NC | D  | NC | D  | D  | NC |    | D  |
| NC          | D  | NC | NC |    | NC |    |    |    | NC |    | NC |
|             | D  | NC | D  |    | D  | NC | NC | NC | NC |    | D  |
| NC          | D  | NC | D  | NC | NC | NC | D  | D  | NC |    | NC |
|             | NC | NC | NC | NC | D  |    | NC | NC | MI |    | NC |
| NC          | NC | NC | NC | NC | NC | NC | NC | NC | NC | NC | NC |
| D           | NC |    | D  | NC |    | NC | NC |    | NC |    | NC |
| NC          | NC |    | NC |    | NC | NC | NC |    | NC |    | D  |
| NC          | D  | NC | D  | NC | NC |    |    | MI | NC | NC | NC |
| NC          | D  |    | D  |    | NC |    | NC |    | NC |    | D  |



Figure 7.

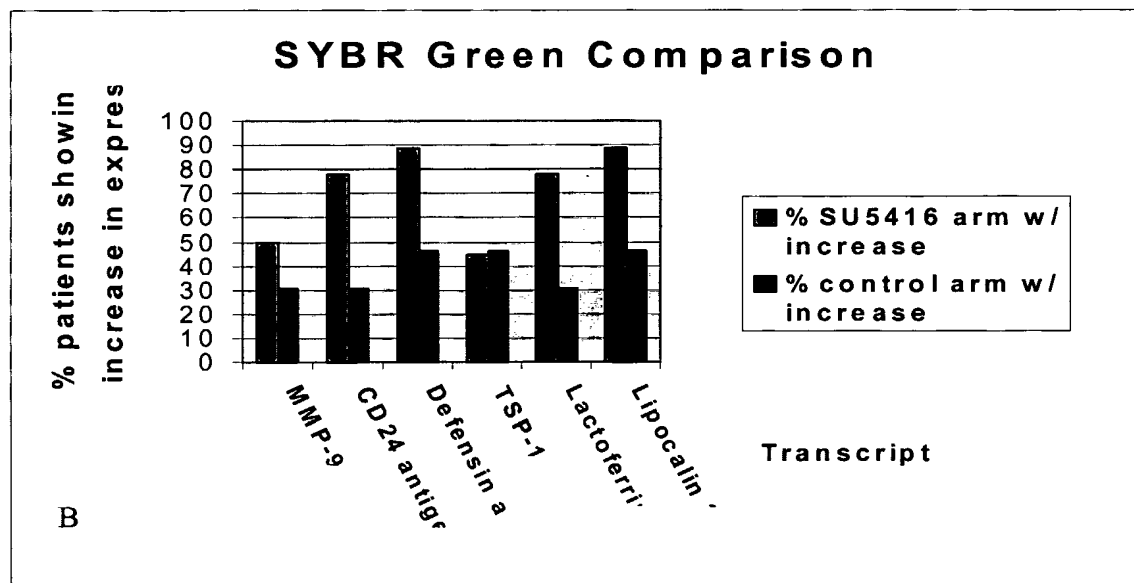
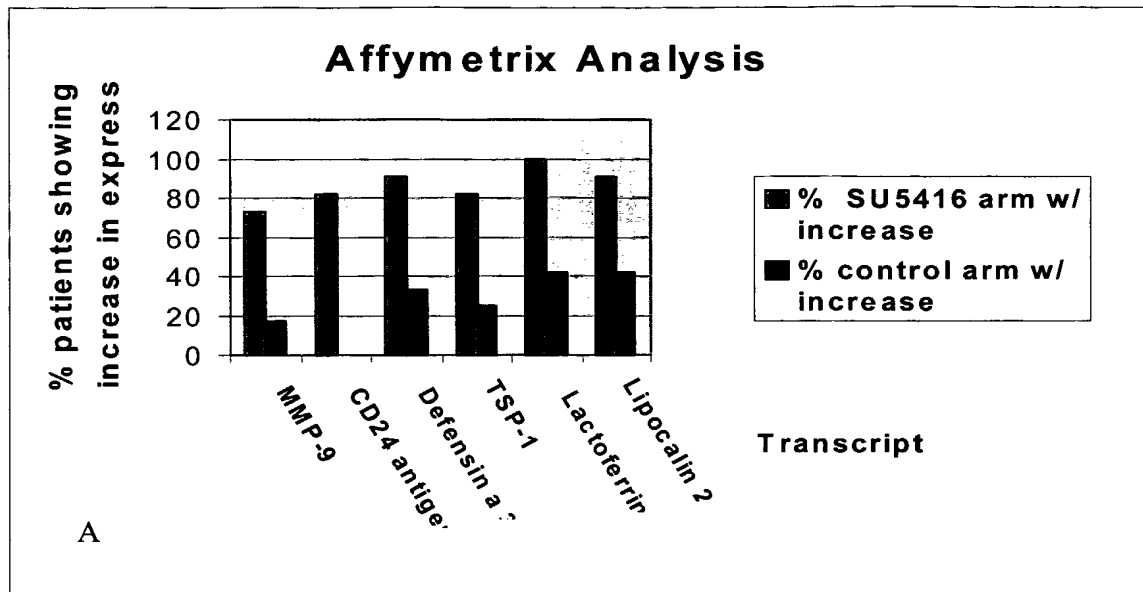


Figure 8.

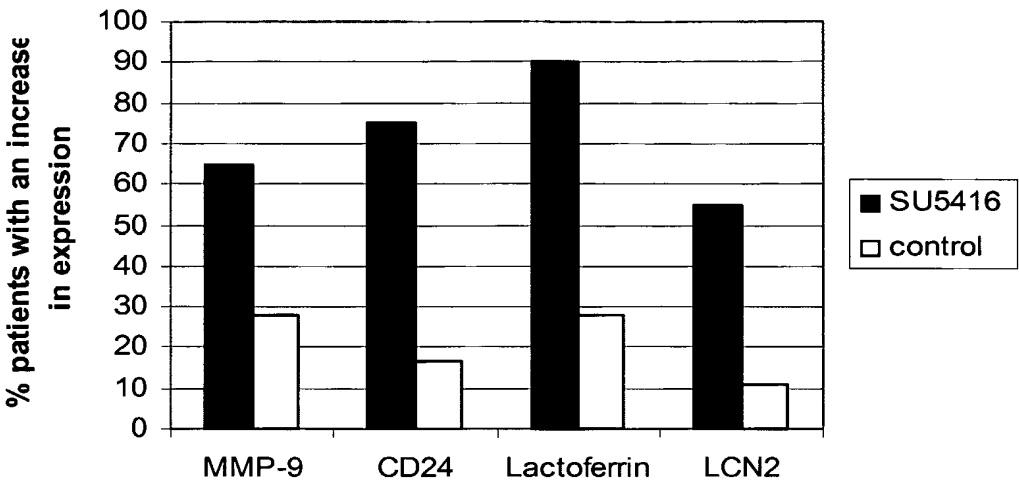


Figure 9.

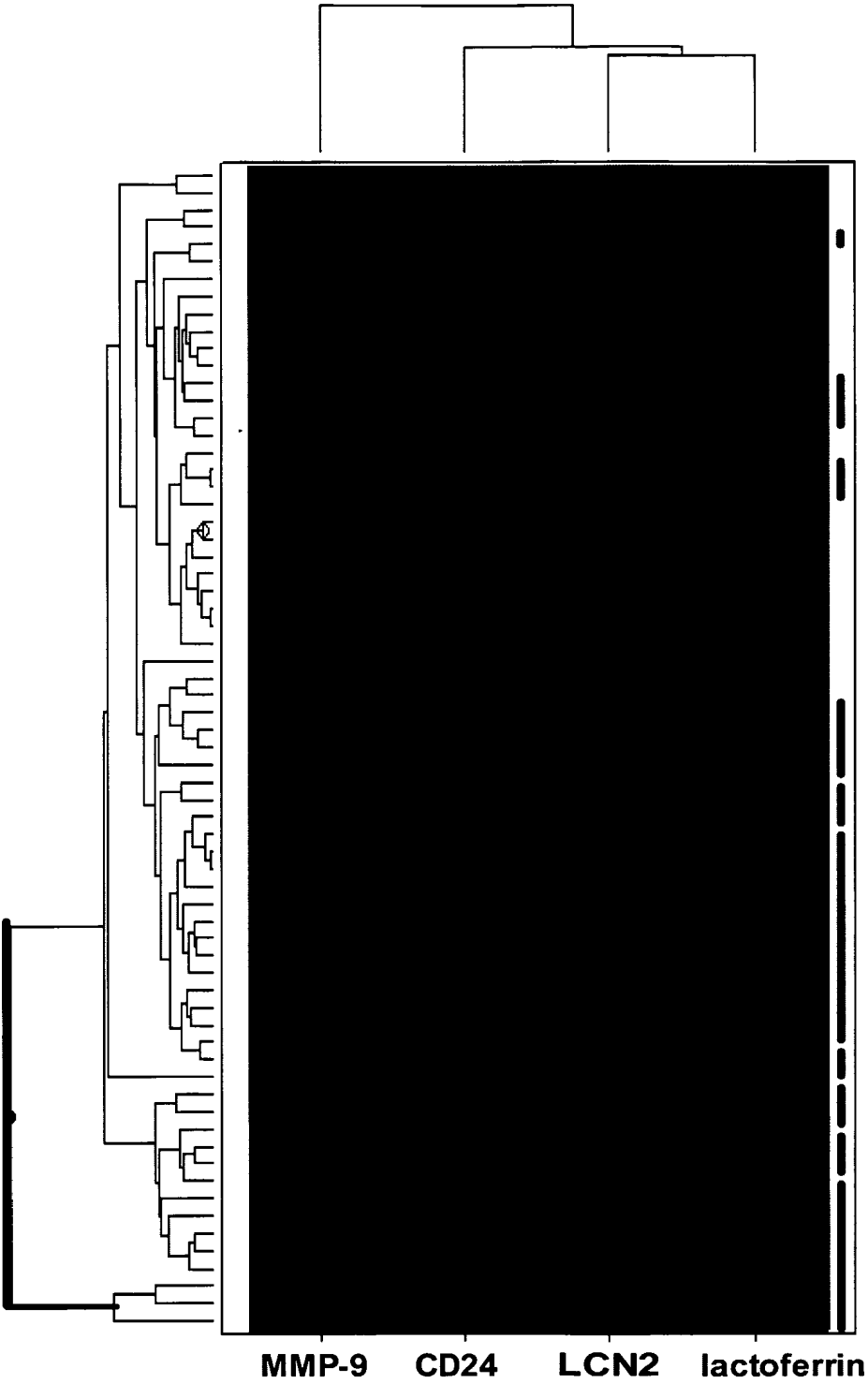
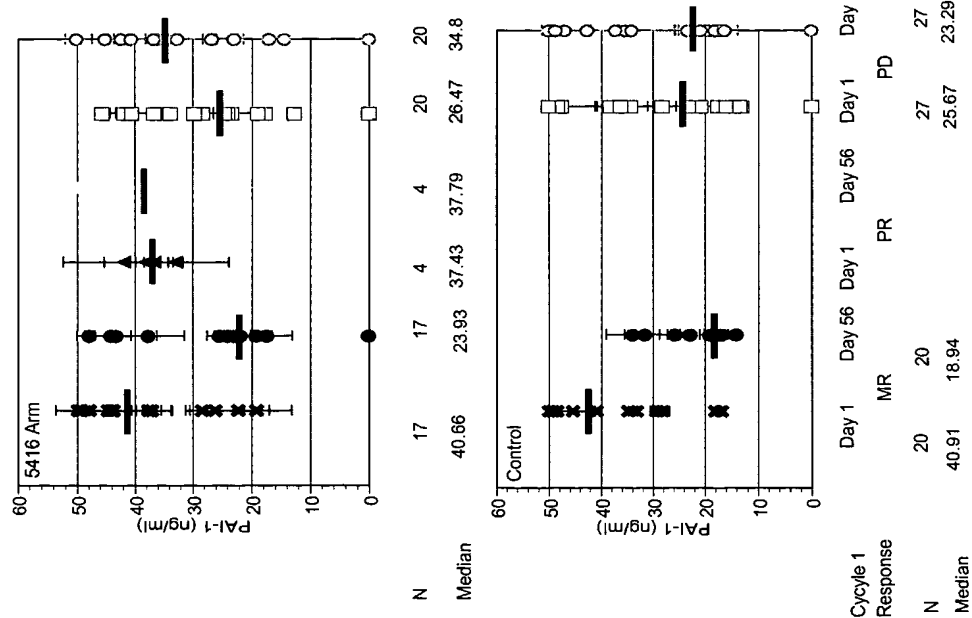


Figure 10.



Median levels of PAL-1 are indicated by a solid bar.  
MR = minor response (cycle 1), PR = partial response (cycle 1), PD = progressive disease (cycle 1).

**Figure 11.****mRNA and protein sequences for human lactoferrin****X53961****Human mRNA for lactoferrin [gi:34415]**

```

1 gactcctagg ggcttcgaga cctagtggga gagaagaac atcgagcag ccaggcagaa
61 ccaggacagg tgagggtgag gctggcttct ctctgcagc gcggtgtgga gtcctgtcct
121 gcctcagggc tttcggagc ctggatcctc aaggaacaag tagacctggc cgcggggagt
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241 gggcaggcgc aagtgcagag cttcgtttg ccaagtccc tccagaccgc agacatgaaa
301 cttgtctccc tcgtcctgct gttcctcggg gccctcggac tgtgtctggc tggccgtagg
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421 caaagggaata tgagaaaagt gctgtggcct cctgtcagct gcataaagag agactcccc
481 atccagtga tccaggccat tgcggaaaac agggccgatg ctgtgacct tgatggtgt
541 ttcatatacg aggcaggcct gggcccctac aaactgcgac ctgtagcggc ggaagtctac
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661 agcttcagc tgaacgaact gcaaggtctg aagtcctgcc acacaggcct tcgaggacc
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1801 tgcaaatgtg atgaatatt cagtcaaagc tgtccccctg ggtctgacc gagatctaat
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1981 gcatttgtga aagatgtcac tgtcttcag aacactgatg gaaataacaa tgaggcatgg
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2521 cctgtgaag gtgggagtg cccatccatc tgcttaaat tccctgctgt cgtcttagca
2581 agaagtaaaa tgagaaattt tttgatatt caaaaaaa

```

**Protein sequence of human lactoferrin**

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GTERQPRTHYYAVAVVKKGGSFQLNELQGLKSCHTGLRRTAGWNVPTGTLRPFLNWTG  
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PVEGYLAVAVVRRSDTSLTWNSVKGKKSCHTAVDRTAGWNIPMGLLFNQTGCKFDEY  
FSQSCAPGSDPRSNLCALCIGDEQGENKCVPSNERYYGYTGAFRCLAENAGDVA FVK  
DVTVLQNTDGNNNEAWAKDLKLADFALLCLDGKRKPVTEARSCHLAMAPNHAVVSRMD  
KVERLKQVLLHQQAKFGRNGSDCPDKFCLFQSETKNLLFNDNTECLARLHGKTTYEKY  
LGPQYVAGITNLKKCSTSPLEACEFLRK

**mRNA and protein sequences for human lipocalin-2 (LCN2)**

NM\_005564

Homo sapiens lipocalin 2 (oncogene 24p3) (LCN2), mRNA [gi:5031852]

```
1 atgccccctag gtctcctgtg gctgggccta gccctgttgg gggctctgca tgcccaggcc
61 caggactcca ctcagacct gatccagcc ccacctctga gcaaggctcc tctgcagcag
121 aactccagg acaaccaatt ccaggggaag tggatgttg taggcctggc aggggaatgca
181 atttcagag aagacaaaga ccgcaaaag atgtatgcca ccatctatga gctgaaagaa
241 gacaagagct acaatgtcac ctccgtctg ttaggaaaa agaagtgtga ctactggatc
301 aggacttttg ttccaggttg ccagcccggc gagttcacgc tgggcaacat taagagttac
361 cctggattaa cgagttacct cgtccgagtg gtgagcacca actacaacca gcatgctatg
421 gtgttcttca agaaagtctc taaaacagg gactacttca agatcacctc ctacgggaga
481 accaaggagc tgacttcgga actaaaggag aacttcacc gcttctccaa atatctgggc
541 ctccctgaaa accacatgt ctccctgtc ccaatcgacc agtgatcga cggtcga
```

**Note:** there is an additional 3' exon, not represented in the mRNA sequence above, that is included in the sequence that Affymetrix used in designing probes for LCN2 expression (and which was used in designing RT-PCR primers). The additional sequence is as follows:

```
1 ggtgccgcca gctgccgac cagccgaac accattgagg gagctgggag accctcccca
61 cagtgccacc catgcagctg ctcccaggc caccgcgtg atggagcccc acctgtctg
121 ctaataaac atgtgc
```

**Protein sequence for human lipocalin-1 (LCN2)**

```
MPLGLLWLGLALLGALHAQAQDSTSDLIPAPPLSKVPLQQNFQD
NQFQ GKWYVVG LAGNAILREDKDPQKMYATYELKEDKSYNVTSVLFRKKKCDYWIRT
FVPGCQPGFTLGNIKSYPLTSLVVRVSTNYNQHAMVFFKKVSQNREYFKITLYGR
TKELTSELKENFIRFSKYLGLPENHIVFPVPIDQCIDG
```

**mRNA and protein sequences for human MMP-9**

**NM\_004994** **Homo sapiens matrix metalloproteinase 9 (gelatinase B, 92kD gelatinase, 92kD type IV collagenase) (MMP9), mRNA [gi:482835]**

```

1 agacacctct gccctcacca tgagcctctg gcagcccttg gtcctggtgc tcttggtgct
61 gggctgtgct tttctgccc ccagacagcg ccagtccacc ctgtgtctct tccttgaga
121 cctgagaacc aatctcaccg acaggcagct ggacagaggaa tacctgtacc gctatggta
181 cactcgggtg gcagagatgc gtggagagtc gaaatctctg gggcctgcgc tctgcttct
241 ccagaagcaa ctgtccctgc ccgagaccgg tgagctggat agcgccacgc tgaaggccat
301 gcgaacccca cggtcgggg tcccagacct gggcagattc caaacctttg agggcgacct
361 caagtggcac caccacaaca tcacctattg gatccaaaac tactcggaag acttgccgcg
421 ggcggtgatt gacgacgct tggccgcgc ctcgcactg tggagcgcgg tgacccgct
481 caccttcact cgcgtgtaca gccgggacgc agacatcgtc atccagttg gtgtcgcgga
541 gcacggagac gggatccct tcgacgggaa ggacgggctc ctggcacacg ccttctctc
601 tggccccggc attcaggag acgcccattt cgacgatgac gaggttggt ccttggcaa
661 gggcgtctgt gttccaact ggtttgaaa cgcagatggc gcggcctgcc acttccctt
721 catctcgag ggcgctct actctgctg caccaccgac ggtcgtccg acggcttgc
781 ctggtgcagt accacggcca actacgacac cgacgaccgg ttggcttct gcccagcga
841 gagactctac acccgggacg gcaatgtga tgggaaacc tccagtttc cattcatct
901 ccaaggccaa tctactccg cctgcaccac ggacggtcgc tccagggct accgctggtg
961 cgccaccacc gccaactag accgggacaa gctcttcggc ttctgcccga cccgagctga
1021 ctgacgggtg atggggggca actcggcggg ggagctgtgc gtcttccct tcatttctc
1081 gggtaaggag tactcgacct gtaccagcga gggccgcgga gatgggcgcc tctggtgcgc
1141 taccacctcg aacttgaca gcgacaagaa gtggggcttc tgcccggacc aagdatacag
1201 ttgttctc gtggcggcgc atgagttcgg ccacgcgctg ggcttagatc attctcagt
1261 gccggaggcg ctcattgacc ctatgtaccg ctctactgag gggcccccct tgcataagga
1321 cgactggaat ggcacggc acctctatgg tctcgcct gaacctgagc caggcctcc
1381 aaccaccacc acaccgcagc ccacggctcc ccgacggtc tgcccaccg gacccccac
1441 tgtccacccc tcagagcgcc ccacagctgg cccacaggt ccccccctcag ctggccccc
1501 aggtccccc actgctggcc cttctacggc cactactgtg ctttgagtc cgggtggacga
1561 tgcttgaac gtgaacatct tcgacccat cgcggagatt gggaaccagc tgtattgtt
1621 caaggatggg aagtactggc gattctctga gggcaggggg agccggccgc agggcccctt
1681 ccttatcgcc gacaagtggc ccgcgctgcc ccgcaagctg gactcggct ttagaggacc
1741 gctctccaag aagcttttct tcttcttg gcgccaggtg tgggtgtaca caggcgcgtc
1801 ggtgctgggc ccgagggctc tggacaagct gggcctggga gccgacgtg cccaggtgac
1861 cggggccctc cgagtgga gggggaagat gctgctgttc agcggcgcc gcctctggag
1921 gttcgacgtg aaggcgaga tggtgatcc ccggagcgc agcgaggtg accggaatt
1981 cccgggggtg ctttggaca cgcacgacgt cttccagtac cgagagaaag cctatttctg
2041 ccaggaccgc ttctactggc gcgtgagttc ccgagtgag tgaaccagg tggaccaagt
2101 gggctacgtg acctatgaca tctgcagt ccctgaggac tagggctccc gtctgcttt
2161 gcagtccat gtaaatccc actgggacca accctgggga aggagccagt ttgccggata
2221 caaactggta ttctgttctg gaggaaggg aggagtgag gtgggctggg ccctctctc
2281 tcaccttgt ttttgttg agtgttcta ataaacttg atttctaac cttt

```



**Protein sequence for Homo sapien MMP9**

MSLWQPLVLVLLVLGCCFAAPRQRQSTLVLFPGDLRTNLTDRQL  
AEEYLYRYGYTRVAEMRGESKSLGPALLLLQQLSLPETGELDSATLKAMRTPRCGVP  
DLGRFQTFEGDLKWHHHNITYWIQNYSEDLPRAVIDDAFARAFALWSAVTPLTFTRVY  
SRDADIVIQFGVAEHGDGYFPDGDGLLAHAFPPGPGIQGDAHFDDELWSLGKGVV  
PTRFGNADGAACHFPFIFEGRSYSACTTDGRSDGLPWCSTTANYDTDDRFGFCPSERL  
YTRDGNADGKPCQFPFIFQGQSYSACTTDGRSDGYRWCATTANYDRDKLFGFCPTRAD  
STVMGGNSAGELCVFPFTFLGKEYSTCTSEGRGDGRLWCATTSNFDSDDKKWGFCPDQG  
YSLFLVAAHEFGHALGLDHSSVPEALMYPMYRFTEGPPLHKDDVNGIRHLYGPRPEPE  
PRPPTTTTPQPTAPPTVCPTGPPTVHPSERPTAGPTGPPSAGPTGPPTAGPSTATTVP  
LSPVDDACNVNIFDAIAEIGNQLYLFKDGKYWRFSEGRGSRPQGPFLIADKWPALPRK  
LDSVFEEPLSKKLFFFSGRQVWVYT GASVLGPRRLDKLGLGADVAQVTGALRSGRGKM  
LLFSGRRLWRFDVKAQMVDPRSASEVDRMFPGVPLDTHDVFQYREKAYFCQDRFYWRV  
SSRSELNQVDQVG YV TYDILQCPED

**mRNA and protein sequences for human CD24****L33930 Homo sapiens CD24 signal transducer mRNA, complete cds and 3' region [gi:500848]**

1 cggttctcca agcaccacgc atcctgctag acgcgccgcg caccgacgga ggggacatgg  
61 gcagagcaat ggtggccagg ctggggctgg ggctgctgct gctggcactg ctctaccca  
121 cgcagattta ttccagtga acaacaactg gaacttcaag taactcctcc cagagtactt  
181 ccaactctgg gttggcccca aatccaacta atgccaccac caaggcggct ggtggtgccc  
241 tgcagtcaac agccagtcct ttcgtggctc cactctctct tctgcatctc tactcttaag  
301 agactcagcg caagaaacgt cttctaaatt tcccacatct ctaaacccaa tccaaatggc  
361 gtctggaagt ccaatgtggc aaggaaaaac aggtcttcat cgaatctact aattccacac  
421 cttttattga cacagaaaat gttgagaatc ccaaatttga ttgatttga gaacatgtga  
481 gaggtttgac tagatgatga atgccaatat taaatctgct ggagtttcat gtacaagatg  
541 aaggagagcg aacatccaaa atagttaaga catgatttcc ttgaatgtgg cttgagaaat  
601 atggacactt aatactacct tgaataaag aatagaataa aaggatggga ttgtggaatg  
661 gagattcagt ttctattgtt tcattaattc tataaggcca taaaacaggt aatataaaaa  
721 gttccatcg atctatttat atgtacatga gaaggatcc ccagggtgta ctgtaattcc  
781 tcaacgtatt gtttcgacgg cactaattta atgccgatat actctagatg aatgtttaca  
841 ttgttgagct attgctgttc tcttggaac tgaactcact ttctctga ggctttggat  
901 ttgacattgc atttgacctt ttaggtagta attgacatgt gccagggcaa tgaatgaatg  
961 gaatctacc cagatccaag catcctgagc aactcttgat tatccatatt gagtcaaatg  
1021 gtaggcattt cctatcacct gtttccattc aacaagagca ctacattctt ttgctaaac  
1081 ggattccaaa gagtagaatt gcaatgacca cgaactaatt caaatgctt ttattatta  
1141 ttatttttta gacagtctca cttgtcgcc caggccggag tgcagtgggt cgatctcaga  
1201 tcagtgtacc atttgctcc cgggctcaag cgattctcct gcctcagcct cccaagtagc  
1261 tgggattaca ggcacctgcc accatgcccg gctaattttt gtaattttag tagagacagg  
1321 gtttcacat gttgccagg ctggtttaga actcctgacc tcaggtgatc caccgcctc  
1381 ggctcccaa agtgcctgga ttacaggctt gagccccgc gccagccat caaatgctt  
1441 ttatttctg catatgtttg aatactttt acaatttaa aaaatgatct gtttgaagg  
1501 caaaattgca aatcttgaaa ttaagaaggc aaaatgtaa ggagtcaaac tataaatcaa  
1561 gtatttggga agtgaagact ggaagctaatt ttgcataaat tcacaaactt ttactctt  
1621 tctgtatata cattttttt ctttaaaaa caactatgga tcagaatagc aacatttga  
1681 acactttttg ttatcagtca atatttttag atagttaga cctggctcta agcctaaaag  
1741 tgggcttgat tctgcagtaa atcttttaca actgcctcga cacacataaa cttttttaa  
1801 aatagacact ccccgaaagc tttgtttgt atggcacac actgatgctt agatgttcca  
1861 gtaatcta atggccacag tagtcttgat gaccaaagct cttttttcc atctttaga  
1921 aactacatgg gaacaaacag atcgaacagt ttgaagcta ctgtgtgtgt gaatgaacac  
1981 tcttgcttta ttccagaatg ctgtacatct attttgatt gtatatgtg gttgtgtatt  
2041 tacgcttga tcatagtaa cttcttatgg aattgatttg cattgaacga caaactgtaa  
2101 ataaaaagaa acggtg

**Protein sequences for human CD24**

MGRAMVARLGLGLLLLALLLPTQIYSETTTGTSSNSSQSTSNS  
GLAPNPTNATTKAAGGALQSTASLFVVSLSLLHLYS

**Figure 12. (Page 1 of 33)**

D30655. Homo sapiens mRNA...[gi:485387]:

Eukaryotic initiation factor 4AII

DNA sequence:

```

1 gtggttttc ggatcatgic tgggtggctcc gcggattata acagagaaca tggcggccca
61 gagggaaatg accccgatgg tgcacatgag agcaactgga atgagattgt tgataacttt
121 gatgatatga atttaaagga gtctctcctt cgtggcatct atgcttacgg ttttgagaag
181 ccttccgcta ttcagcagag agctattatt cctgtatta aagggtatga tggattgct
241 caagctcagt caggactgga caagacagcc acatttgcta ttccatcct gcaacagttg
301 gagattgagt tcaaggagac ccaagcacta gtattggccc ccaccagaga actggctcaa
361 cagatccaaa aggttaattct ggcacttga gactatatgg gagccactg tcatgcctgc
421 attggtgaa aatgattctg aaatgaaatg caaaaactgc aggtgaagc accacatatt
481 gttgttgga caccggggag agtgtttgat atgttaaaca gaagatacct ttctccaaa
541 tggatcaaaa tgtttgttt ggaagaagca gatgaaatgt tgagccgtgg tttaaggat
601 caaatctatg agattttcca aaaactaaac acaagtattc aggttggttt tgctctgcc
661 acaatgcaa ctgatgtgtt ggaagtgacc aaaaaattca tgagagatcc aattcgaatt
721 ctggtgaaaa aggaagaatt gaccctgaa ggaatcaaac agttttatat taatgttgag
781 agagaggaat ggaagtggga tacactttgt gactgtacg agacactgac cattacacag
841 gctgttattt ttcaatac gaggcgaag gtggactggc tgactgagaa gatgatgcc
901 agagacttca cagtttctgc tctgatgtt gacatggacc agaaggagag agatgttatc
961 atgagggaa tccggtcagg gtcaagtcgt gttctgatca ctactgactt gttggctcgc
1021 gggattgatg tgcaacaagt gtctttggtt ataaattatg atctacacac caatcgtgaa
1081 aactatattc acagaattgg cagagggggt cgatttgga ggaagggtt ggctataaac
1141 tttgttactg aagaagacaa gaggattctt cgtgacattg agactttcta caatactaca
1201 gtggaggaga tgcccatgaa tgggctgac cttatthaat tcctgggatg agagttttg
1261 atgcagtgtc cgtgtgtgt gaataggcga tcacaacgtg cattgtgctt cttctttg
1321 gaatatattg atctgtctc aatgctcata acggatcaga aatacagatt ttgatagcaa
1381 agcgacgtta gtcgtgagct cttgtgagga aagtcattgg cttatcctc tttagagta
1441 gactgtggg gtgggtataa aagatggggt ctgtaaaatc ttctttctt agaaattat
1501 ttctagttc ttagaaaatg gttgtattag atgttctcta tcatttaata atatactgt
1561 ggactaaaag alataagtc tgataaaaat cagccaatta tgttaacta gcatactgc
1621 ctttattgtg ttgtcatta gcctgagtag aaaggcctt aaaattttt tagaaagcat
1681 ttgaatgcat ttttttgtt attgtattta ttcaataaag tatttaatta gtgctaagt
1741 tgaactggac cctgttgcta agccccagca agcaatccta ggtagggtt aatccccagt
1801 aaaattgcca tattgcacat gtctaatga agtttgaatg taaataaat tgtatattca
1861 cttt

```

protein sequence:

```

MSGGSADYNREHGGPEGMDPDGVIESNWNEIVDNFDDMNLKESLLRGIYAYGF EKPSAIQQRAIIPC IKGYDVIAQAQ
SGTGKTATFAISILQQLEIEFKETQALVLAPTRELAQQIQKVILALGDYMGATCHACIGGTNVRNEMQKLQAEAPHIVVG
TPGRVFDMLNRRYLSPKWIKMFVLDEADEMLSRGFKDQIYEIFQKLNTS IQVVFASATMPTDVLVETKKFMRDPIRILV
KKEELTLEGIKQFYINVEREEWKDLTCLDYETLTITQAVIFLNTRRKVDWLTEKMHARDFTVSALHGDMDQKERVIM
REFRSGSSRVLITDLLARGIDVQQVSLVINYDLPTNRENYIHRIGRGGFRGRKGVAINFVTEEDKRILRDIETFYNTTVE
EMPMNVADLI

```

**Figure 12. (Page 2 of 33)**

M92383. Homo sapiens thym...[gi:339696]:

Homo sapiens thymosin beta-10 gene

DNA sequence:

```
1 cgtcctacat ctgcgcata cagccacg tgcgcacatc actgggggtg ccncgggaga
61 cagagccgct ggtagcctaa ggnngggggg cagccaggag aaagccccgc cgctgctgt
121 cccgcccctc gggtgccagc accgcccctg ctgcggcggg tgaggggcgg ggcggggccg
181 cggcgtatat aaggctaggc ggggcgccgc tctttgtt ctgctgcag caacgcgagt
241 gggagcacca ggtctcggg ctcggaacga gactgcacgg tgacgtgacg gccgggcggg
301 ggcccagggt gtggtcggat cgggtgcacc gcgggcgcgc aaccgggaca ggcgttctc
361 ggaccggacg cagggggccg gaccacgccc tgggaccgag aagaggggtg cggacgcgcc
421 cagatcctcg gcctggggc tgctcggcag cctggcgcg agtgccacgt cgagaggcgt
481 cggcggggag cgcggaagg gacggcctgc gccaggccc aggtcaagcg ccttggttg
541 cccactagga ttgtttaag aaaatggcag acaaaccaga catgggggaa atcgccagct
601 tcgataaggc caagctgaag aaaacggaga cgcaggagaa gaacaccctg ccgaccaaag
661 agagtgaagt tgctcggtc tccgcgcccc agcccagccc ctaccctgc tctccttgc
721 aaaccacac ctccacccc cccccgccg ttgtcccgg tgtggcggc cccggcactc
781 tticagttc acaaagcgc ttgttctcc ccagcccaa gcttcttct aaatcccaca
841 cctcgtggtg ctatcacac cgggaagcac ctcggtgcg ggtgggggtg tgcagcnccc
901 ctccagcgcc cgttccgtc tcaagccatt gagcaggaga agcggagtga aattcctaa
961 gatcctggag gatttctac ccccgtctc tcggagcacc ccagtcgctg atgtggagaa
1021 gagccacct gcaagatgga cagagtcca caagctgcac tgtgaacctg cgagcccgcg
1081 ccgatgccac cggcctgtgg tcgtctgaag ggaccccc ccaatcggac tgccaaattc
1141 tcggtttgcc ccgggatatt atagaaaatt attgtatga ataataaaaa taaaacacac
1201 ctggtggca tggctggcg tggctgagt gtttagtta gtatgggtgc agtcactgc
1261 ag
```

protein sequence:

DCFKKMADKPDMEIASFDKAKLKTETQEKNLPTKETIEQEKRSIS

**Figure 12. (Page 3 of 33)**

X79536. H.sapiens mRNA fo...[gi:496897]:

H.sapiens mRNA for hnRNPcore protein A1

DNA sequence:

```
1 ttaaagtctc tcttcacct gccgtcatgt ctaagtcaga gtctcctaaa gagcccgaac
61 agctgaggaa gctcttcatt ggagggttga gcttgaac aactgatgag agcctgagga
121 gccatttga gcaatggga acgctcacgg actgtgtgt aatgagagat ccaaaccaca
181 agcgctctag gggctttggg ttgtcacat atgccactgt ggaggagggt gatgcagcta
241 tgaatgcaag gccacacaag gtggatggaa gattgttga accaaagaga gctgtctcca
301 gagaagattc tcaaagacca ggtgccact taactgtgaa aaagatattt gttgtggca
361 ttaaagaaga cactgaagaa catcacctaa gagattattt tgaacagtat ggaaaaattg
421 aagtattga aatcatgact gaccgaggca gtggcaagaa aaggggcttt gccttataa
481 cctttgacga ccatgactcc gtggataaga ttgtcatca gaaataccat actgtgaatg
541 gccacaactg tgaagttaga aaagccctgt caaagcaaga gatggctagt gcttcatcca
601 gccaaagagg tcgaagtgt tctggaaact ttgggtgtgg tcgtggaggt ggttcggtg
661 ggaatgacaa ctcggtcgt ggaggaaact tcagtgtcgt tgggtgcttt ggtggcagcc
721 gtgtgtgtgg tggatatgtt ggcagtgggg atggctataa tggatttggc aatgatggaa
781 gcaattttg aggtgttga agctacaatg attttggaa ttacaacaat cagtctcaa
841 attttgacc catgaaggga ggaattttg gaggcagaag ctctggcccc tatggcgtg
901 gaggccaata ctttcaaaa ccacgaaacc aagggtgcta tggcggttcc agcagcagca
961 gtagctatgg cagtggcaga agattttaa tagggaggag tctgctacta gtcttatcag
1021 ctcttaaaaa cagaaactca tctgtccaag ttcgtggcag aaaggaacgt ccttgtgaag
1081 accttatct gagccactgt acttcgttat cagccatgc agttacatg agctgtctg
1141 cagctcgaaa ttccattttg tgaatgggt ttttttta ataaactga ttaactt
```

protein sequence:

```
MSKSESPKEPEQLRKLFIGGLSFETTESLRSHFEQWGTLTDCVVMRDPNTRSRGFGFVYATVEEVDAAMNARP
HKVDGRVVEPKRAVSREDSQRPGAHLTVKKIFVGGIKEDTEEHHLRDYFEQYGKIEVIEIMTDRGSGKKRGFAFVTFD
DHDSVDKIVIQKYHTVNGHNCEVRKALSKQEMASASSSQRGRSGSNFGGGRGGGFGGNDNFRGGNFSGRGGF
GGSRRGGGYGGSGDGYNGFGNDGSNFGGGGSYNDFGNYNQSSNFGPMKGGNFGGRSSGPYGGGGQYFAKP
RNQGGYGGSSSSSYSGRRF
```

**Figure 12. (Page 4 of 33)**

X14046. Human mRNA for le...[gi:29793]:

Human mRNA for leukocyte antigen CD37

DNA sequence:

```
1 gctcccca ctgtcagcac ctctctgtg tggtagtg accgctacc ccactaggtg
61 aagatgtcag cccaggagag ctgcctcagc ctcatcaagt acttctctt cgtttcaac
121 ctctcttct tcttctcgg cagcctgac ttctgctcg gcatctggat cctcatcgac
181 aagaccagct tctgtcctt tgtgggctg gcctcgtgc ctctcgat ctgtccaaa
241 gtcctggcca tctcaggaat cttaccatg ggcacgccc tctgggttg tggggggcc
301 ctaaggagc tccgtgcct cctgggctg tatttggga tctgctgt cctgtttgcc
361 acacagatca cctgggaat cctcatctcc actcagcggg cccagctga gcaagcttg
421 cgggacgtcg tagagaaaac catccaaaag tacggacca acccgagga gaccgggcc
481 gaggagagct gggactatgt gcagttccag ctgcgtgct gcggtggca ctaccgcag
541 gactggttcc aagtctcat cctgagaggt aacgggtcgg aggcgcaccg cgtgccctgc
601 tctgtctaca actgtcggc gaccaacgac tccacaatcc tagataaggt gatctgccc
661 cagctcagca ggcttgaca cctggcgcgg tccagacaca gtgcagacat ctgcgtgtc
721 cctgcagaga gccacatcta ccgcgagggc tgcgcgagg gcctccagaa gtggctgcac
781 aacaacctta ttccatagt gggcatttgc ctgggcgtcg gcctactga gctcgggtc
841 atgacgctct cgatattct gtgcagaaac ctggaccacg tctacaaccg gctcgtcga
901 tacggttag ccccgccctc cccaaagtcc cgcgccgcc cgtcacgtg cgtggggcac
961 ttccctgtg ctgtaaata ttgtttaat cccagttcg cctggagccc tccgcctca
1021 cattcccctg gggaccacg tggctgcgtg ccctgtctg tgcacctct cccacgggac
1081 ctggggcttt cgtccacagc ttctgtccc catctgtcg cctac
```

protein sequence:

```
MSAQESCLSLIKYFLVFVNLFFFVLGSLIFCFGIWILIDKTSFVSFVGLAFVPLQIWSKVLAI SGIFTMGIALLGCVGALKEL
RCLLGLYFGMLLLLFATQITLGILISTQRAQLERSLRDVVEKTIQKYGTNPEETA AEESWDYVQFQLRCCGWHYPQDW
FQVLILRGN GSEAH RVP CSCYNLSATNDSTILDKVILPQLSRLGHLARSRHSADICAVPAESHIYREGCAQGLQKWLHN
NLISIVGICLGVLLELGFMTLSIFLCRNLDHVYNRLARYR
```

**Figure 12. (Page 5 of 33)**

M32578. Human MHC class I...[gi:188305]:

Human MHC class II HLA-DR beta-1

DNA sequence:

```
1 agtttcctt gagtgagact tgctgtctt tctggccctt ggtcctgtt ttttccag
61 catggttgt ctgaagctt ctggagggtt ctacatggc gtgctgacg tgacactgat
121 ggtgctgagc tccccactg ctttggttg ggacacccga ccatgtttt tgcagcagga
181 taagtatgag tgcattttt tcaacgggac ggagcgggtg cggttcctg acagaggcat
241 ctataaccaa caggagaacg tgcgcttca cagcgacgtg ggggagtacc gggcggtagc
301 ggagctgggg cggcctgacg ctgagtactg gaacagccag aaggacatcc tggagcaggc
361 gcggggccgc gtggacacct actgcagaca caactacggg gctgtggaga gcttcacagt
421 gcagcggcga gttgagccta aggtgactgt gtatcctgca aggacccaga cctgcagca
481 ccacaacctt ctggtctgct ctgtgaatgg ttctatcca ggcagcattg aagtcagggtg
541 gttccggaac ggccaggaag agaaggctgg ggtggtgtt acaggcctga ttcagaatgg
601 agactggacc ttccagattc tggtagtct ggaaacagtt cctcggagtg gagaggttta
661 cacctgcaa gtggagcacc caagcgtgac gagccctctc acagtggaat ggagagcaca
721 gtctgaatct gcacagagca agatgctgag tggaaatcgg ggctttgtc tgggcctgct
781 cttccttggg gccgggctat tcatctact caagaatcag aaagggcact ctggacttca
841 cccaacagga ctgtagact gaagtcaga tgaccacatt caagggggaa ccttctgccc
901 cagctttgca tgatgaaaag ctttctgct tggctcttat tctccaca gagaggactt
961 tctcaggccc tggttgctc cggttcagca actctgcaga aaatgtccat ccttgtggct
1021 tctcagctc ctgcccttg cctgaagtcc cagcattgat ggcagtgcct catctcaac
1081 ttagtgctc cctttacct aaccctacg cctccatgc atctgtact cccctgtgcc
1141 acaaatggac tacgttatta aattttctg aagcccagag ttaaaaatca tctgtccacc
1201 tggcaccaaa gacaaa
```

protein sequence:

```
MVCLKLPGGSYMAVLTVTLMVLSSPLALAGDTRPCFLQQDKYECFFNGTERVRFHLHRGIYNQQENVRFDSDVGEY
RAVTELGRPDAEYWNSQKDILEQARAAVDTYCRHNYGAVESFTVQRRVEPKVTVYPARTQTLQHHNLLVCSVNGFY
PGSIEVRWFRNGQEEKAGVVSTGLIQNGDWTFQILVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRAQSESAQSKM
LSGIGGFVLGLLFLGAGLFYFKNQKGHSGHLPTGLVS
```

**Figure 12. (Page 6 of 33)**

U54558. Homo sapiens tran...[gi:2351377]:

Homo sapiens translation initiation factor eIF3 p66 subunit mRNA

DNA sequence:

```

1 gaattcggca cgagctaacg cgggtcccg cgcgacccat ctgttgccat cccggccggc
61 cgaggccatt gcagattttg gaagatggca aagttcatga caccctgat ccaggacaac
121 ccctcaggct ggggtccctg tgcggttccc gagcagtttc gggatatgcc ctaccagccg
181 ttcagcaaag gagatcggct aggaaggtt gcagactgga caggagccac ataccaagat
241 aagaggtaga caataagta ctctctcag ttgtgtgtg gaagtaata tgcttattc
301 catgaggagg atgaaagtag ctccagctg gtggatacag cgcgcacaca gaagacggcc
361 taccagcgga atcgaatgag atttgcccag aggaacctcc gcagagacaa agatcgtcgg
421 aacatgttgc agtcaacct gcagatcctg cctaagatg ccaaacagaa agagagagaa
481 cgcattcgac tgcagaaaaa gtccagaaa caattgggg ttaggcagaa atgggatcag
541 aaatcacaga aaccccgaga ctctcagtt gaagttcgtg gtgattggga agtgaaagag
601 gaaatggatt ttctcagtt gatgaagat cgctacttgg aagatcaga gccacaggac
661 attgagtgtt gtggggccct agaatactac gacaaagcct ttgaccgat caccacgagg
721 agtgagaagc cactcgggag catcaagcgc atctccaca ctgtcaccac cacagacgac
781 cctgtcatcc gcaagctggc aaaaactcag gggaatgtgt ttgccactga tgccatcctg
841 gccacgtga tgagctgtac ccgctcagtg tattctggg atattgtcgt ccagagagtt
901 gggaccaaac tcttcttga caagagagac aactctgact ttgacctct gacagttagt
961 gagactgcca atgagcccc tcaagatgaa ggtaattcct tcaattcacc ccgcaacctg
1021 gccatggagg caacctacat caaccacaat ttctccagc agtgcttgag aatggggaag
1081 gaaagatata acttcccaa ccaaacccg ttgtggagg acgacatgga taagaatgaa
1141 atcgctctg ttgcgtaccg ttaccgagg tggaagcttg gagatgatat tgaccttatt
1201 gtccgtgtg agcacgatgg cgtcatgact ggagccaacg gggaagtgtc ctcatcaac
1261 atcaagacac tcaatgagtg ggattccagg cactgtaatg gcgttgactg gcgtcagaag
1321 ctggactctc agcagggggc tgcattgcc acggagctga agaacaacag ctacaagttg
1381 gcccgttga cctgctgtg ttgctggct ggaatcaggt acctcaagct tggttatgtg
1441 tctcgttacc acgtgaaaga ctctcacgc cagtcaccc taggcacca gcagttcaag
1501 cctaagagt ttccagcca gatcaacctg agcgtggaga atgctgggg cattttacgc
1561 tgcgcatag acatctgcat gaagctggag gagggcaat acctatcct caaggacccc
1621 aacaagcagg tcatccgtgt ctacagcctc cctgatggca cctcagctc tgatgaagat
1681 gaggaggaag aggaggagga agaagaggaa gaagaagagg aagaaactta aaccagtgat
1741 gtggagctgg agttgtcct tccaccgaga ctacgagggc cttgatgct tagtggaatg
1801 tgtgtctaac ttgtctctg acatttagca gatgaaataa aatatatc tgtttagtct
1861 ttaaaaaaa aaaaaaaaaa a

```

Protein sequence:

```

MAKFMTPVIQDNPSGWGPCAVPEQFRDMPYQPFSKGDRLGKVADWTGATYQDKRYTNKYSSQFGGGSQYAYFHE
EDESSFQLVDARTQKTAYQRNMRFAQRNLRRDKDRNMLQFNLQILPKSAKQKERERIRLQKKFQKQFQVVRQKW
DQKSQKPRDSSVEVRSDWEVKEEMDFPQLMKMRYLEVSEPQDIECCGALEYDYKAFDRITRSEKPLRSIKRIFHTVT
TTDDPVIRKLAKTQGNVFATDAILATLMSCTRSVYSWDIVVQVRVGSKLFFDKRDNSDFDLTVSETANEPQDEGNSF
NSPRNLAMEATYINHNFSQQCLRMGKERYNFPNPNPFVEDMDKNEIASVAYRYRRWKLGGDDIDLIVRCEHDGVM
T
GANGEVSFINIKTLNEWDSRHCNGVDWRQKLDLSQRGAVIATELKNNSYKLARWTCCALLAGSEYKLGYSRYHYVKD
SSRHVILGTQQFKPNEFASQINLSVENAWGILRCVIDICMKLEEGKYLIKDPNKQVIRVYSLPDGTFSSDEDEEEEEEE
EEEEEEET

```



**Figure 12. (Page 7 of 33)**

X58965. H.sapiens RNA for...[gi:35069]:

H.sapiens RNA for nm23-H2 gene

DNA sequence:

```
1 cggccacgag gcggaatccc ttctgctctc ccagcgcagc gccgcccggc ggcccccca
61 gcttcccga ccatggccaa cctggagcgc acctcatcg ccatcaagcc ggacggcgtg
121 cagcgcggcc tggggggcga gatcatcaag cgcttcgagc agaagggatt ccgcctcgtg
181 gccatgaagt tctccgggc ctctgaagaa cacctgaagc agcactacat tgacctgaaa
241 gaccgacat tctccctgg gctggtgaag tacaagaact cagggccggt tgtggccatg
301 gtctgggagg ggctgaacgt ggtgaagaca gcccagatga tgctgggga gaccaatcca
361 gcagattcaa agccaggcac cattcgtggg gactctgca ttcaggttg caggaacatc
421 attcatggca gtgattcagt aaaaagtgt gaaaaagaaa tcagcctatg gtttaagcct
481 gaagaactgg ttgactacaa gtctgtgct catgactggg tctatgaata agagggtggac
541 acaacagcag tctcctcag cacggcgtgg tgtgccctg gacacagctc ttcattccat
601 tgacttagag gcaacaggat tgatcattct ttatagagc atattgcc aataagcttt
661 tggagccgg
```

protein sequence:

```
MANLERTFIAIKPDGVQRGLVGEIIRFEQKGFRLVAMKFLRASEEHLKQHYIDLKDRPFFPGLVKYMNSGPVVAMVW
EGLNVVKTGRVMLGETNPADSKPGTIRGDFCIQVGRNIIHGSDSVKSAEKEISLWFKPEELVDYKSCAHDWVYE
```

**Figure 12. (Page 8 of 33)**

M17885. Human acidic ribo...[gi:190231]:

Human acidic ribosomal phosphoprotein P0 mRNA

DNA sequence:

```
1 cttctctcgc caggcgtcct cgtggaagt acatcgtctt taaacccct cgtggcaatc
61 cctgacgcac cgccgtgatg cccaggaag acagggcgac ctggaagtcc aactacttc
121 ttaagatcat ccaactattg gatgattatc cgaaatgtt cattgtgga gcagacaatg
181 tgggtccaa gcagatgcag cagatccgca tgtccctcg cggaaggct gtggtgctga
241 tgggaagaa caccatgatg cgcaaggcca tccagggga cctggaaaac aaccagctc
301 tggagaaact gctgcctcat atccggggga atgtgggctt tgtgtcacc aaggaggacc
361 tcatgagat caggacatg ttgctggcca ataagggtcc agctgctgc cgtgctggtg
421 ccattgccc atgtgaagtc actgtgccag cccagaacac tggctcggg cccgagaaga
481 cctcctttt ccaggcttta ggatcacca ctaaaatctc caggggcacc attgaaatcc
541 tgagtgatgt gcagctgatc aagactggag acaaagtggg agccagcgaa gccacgctgc
601 tgaacatgct caacatctcc ccttctcct ttgggtggt catccagcag gtgtcgaca
661 atggcagcat ctacaacct gaagtgttg atatcacaga ggaaacttg cattctgct
721 tcctggaggg tgcgcgaat gttgccagt tctgtctga gattggctac ccaactgtg
781 catcagtagc ccattctatc atcaacgggt acaaacgagt cctggcctg tctgtggaga
841 cggattacac ctccactt gctgaaaagg tcaaggcctt ctggctgat ccatctgcct
901 ttgtggtgc tgcctctgt gctgctgcca ccacagctgc tctgtctgt gctgcagccc
961 cagctaaggt tgaagccaag gaagagtcgg aggagtcgga cgaggatatg ggatttggtc
1021 tcttgacta atcaccaaaa agcaaccaac ttaggcagtt ttattgcaa aacaaggaaa
1081 taaaggctta ctcttt
```

protein sequence:

```
MPREDRATWKSNYFLKIIQLDDYPKCFIVGADNVGSKQMQQIRMSLRGKAVVLMGKNTMMRKAIRGHLENNPALEK
LLPHIRGNVGFVFTKEDLTEIRDMLLANKVPAAARAGAIAPCEVTVPAQNTGLGPEKTSFFQALGITTKISRGTIEILSDV
QLIKTGDKVGASEATLLNMLNISPFSGFLVIQQVFDNGSIYNPEVLDITEETLHSRFLGVRNVASVCLQIGYPTVASVP
HSIINGYKRVLALSVETDYTFPLAEKVKAFLADPSAFVAAAPVAAATTAAPAAAAAPAKVEAKEESEDEDMGFGLFD
```

**Figure 12. (Page 9 of 33)**

X52851. Human cyclophilin...[gi:30167]:

Human cyclophilin gene for cyclophilin

DNA sequence:

```

1  gaattccctt gtaaggtttt cttacaaaa caccagtcac ataagtgcatt ttattttat
61  atttttgttt atttatttga gacggagtcct ctgtctctc aggtcggagt gcagtggcgc
121  catctctgct cgctgcaacc tccacctcct gggttccagc gattctctg cctcagcctc
181  ccgagggggg agctgggact acaggtgcgc accaccatgc ccagctaatt ttgtattttt
241  cgtagagatg ggggttcacc atgtgtcca ggctggtctt gaactcctga cctcaggtga
301  tcttcccgcc tcggcctccc aaagtgtcgg aattacaggc gtgatccacc gcacccggcc
361  tatttttga gagaggggtc cactctgtcg tcccggctgg aatgcagtga tgcgatcacc
421  gccactaca gcctgcacct ccgggctcaa gcaatcctcc ccgcccagcc tctgagtag
481  cgagcgccct gacgcccagc taattttat ttattttat tttttgtag agacggcgctc
541  tctctaagat gcccaggctg gtggccggtg tcgaactcct aagatgaagc gatcctcccc
601  ggccttgccc tcgcgcctc claaagcgcc aggtatgagc caccgcgctt ggcctacaag
661  tgcattttaa ttaaagtatt attaatgtct ttgcctgaag aaattcgctt ttaaattgtg
721  acttatcttt caccacaaaa tcaagcaca attcagcccc gaggcggggg cggtaggagc
781  tggcgggggc gggggcaggg aaagaccagg agcagagatt caaaaagagt aagaggggcaa
841  aatgtgcata atgcactctc acaggtgaag gcctggccag gctcctgttt taatggcttc
901  ctctgaaga agattcaagc agagtgaag atatttctcg aaagtagagc atttgaaaag
961  cattcataaa tcttcaaaaa ccgagagctg ctctgtccc acctcgtag agaaaacagc
1021  gatgtcaaaa ggcaacctcc ttctgacat tgcttggtag gacgcgacgt ggtgtttgcc
1081  cgcgcggaat gcggacgcaa ggctgtcctt aggtctcggg gacgcgcat cccatttcc
1141  gctcgcgag gctgagggtc cggcgcgagg accccagtcg acctgactg gcggcgagc
1201  cttagggcct gcgttcgctt cagttgcccc ctctgtcaa tggggagacg cgcctcatcg
1261  cttagacaac gccgaagagc cgcgcgctt ccgtctccc cgtgcgcgcg ccatgtctgc
1321  caccctcggt ccgactgac cctccccgtt gcccgcgctc ccgtactgcc gcccgcccc
1381  gactccatg ccgcagccac cgcgacggag ccgcgaggcg ggaacctgcc tccgcgctt
1441  agcgcgcacg cgcgcctcat gtgtctctcc catcagcgcc ggcttccgtc tataggccag
1501  atgcactgtc actctggcga agtcgcagac ccgattggcc gggacggagg cgcgagaccg
1561  ggttgcgggc ggggcccgaac gtgtataaaa acgggcggga ggccaggctc gtgcggttt
1621  gcagacgcca ccgcccagga aaacctgtga ctattagcca tggtaaccc caccgtgttc
1681  ttgacattg ccgtcgacgg cgagcccttg ggcgcgctt cctttagggt cggcgggcg
1741  gcggcgctgc ggaatggggc ccagaaagtg ggcgggggtc ggggtgggtg gtacgcccc
1801  aaaggccccg gcgcggggcg acctgcttg agggcgagc gcggcgggc tgcggcgcca
1861  ttctctgacg aggggcaatt ttggagggtc cgcgagtcgc gggaggaggc cgggacgcgg
1921  cggacaaaag caggcggggc ggctgcgagg ccgttggggg agggggcccg cgtccgccc
1981  ccgcctcat gtggccgcgc cctgtctgt ccgacgcacg tgcctggcgg ccgcgctcag
2041  gtccgcgctt tgagagtcgt gtccgcccct agcttggctt gggcgccgca gaccggagcc
2101  agaagcacgc tcgcgggggc ttgcgaccgc ctctctggga agctgtcccc tggcaggcat
2161  ggtgtcttta catctgagc tgggaagctg ttgcttagg ggttttctc aaggatcgag
2221  gcggggtgtg agcccgtcca tgctcggtcc ttagatccc gggaggccat gttataaaag
2281  gagactgtct gggatgtgac ggggtgccac ttgaaatac ttccatttgg ataaagttag
2341  aatatttata catgtgcccc aaacgtccct ccgtgtcccc caccaccaag cggaaatgtg
2401  aaaatggggc ttgctttgct tgggtcccaa ggaccgctt ccactgcagt gacggcgctg
2461  gcgggggagg cgctcttag ccctcccga ttgtccctt ccttagcaag caagtgtcga
2521  ctggccacaa ggcaggcctc ttccgaccaa ggtggattac cagtattac ctaattagt
2581  ttgagagcgt taaatgagt ctaaagatc agttgtaatt atagcatagt atctaaactt
2641  ggcgcgtgtc ttcaaagtta aatattgagt acgattccgt tccagtaac atggatagac
2701  cttagggagt agcgaaatag gatgttagtg gttttattcc tttaaatac atctcaaaag

```

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2761 gccaccaatg gctagttgg atctattcc gaaaatagat tgatcctcat gcagtctcg  
 2821 tgaggacaga gcgatttct tttgcctac cctgtccata gtgcctggca cataggcact  
 2881 gaaacactgc atgttaatcc acaccccacc ccacatga gtgtagtaa agctggtaag  
 2941 tgacaagggc ttctgtgaa acttgccgtg acctaattgt ggcatcagg ttacccaaag  
 3001 agcttcaggg aatgagaaa ggactgcag gcttgatga gaattggagg gtaactgcc  
 3061 atgagggctt tggcttagc gaaagtctga aagggaagcc ataggaactt aaacgtaccg  
 3121 actataaagc tctgagaaaa gctgatgtt tagaaagacc atacattcta ggtacaaata  
 3181 cctaaaaact aaaaaataag tacgttggcc agggggcgcc atcacgaagt caggagattg  
 3241 agaccatctt gggcccctgg tgaaacccca cctctattaa aaatacaaaa attagctggg  
 3301 cgtgggtggc ctgcctgta atctcagcta ctctagaggc tgaggcagga gatcgctga  
 3361 accccggagg cggaggctgc agtgagccga gatcgtgcca ctgcactcca gcctggtgac  
 3421 agcgagactc ttgtctcaaa aaaaaaaaag tacattgcta taagagaagt gcacacggat  
 3481 actagtattg aattcagcta catcttgaa atagcttata aaatgctact ttaaacaag  
 3541 ctgttttat gaaaggcctt gtaaatgtt atggtattta agctacctt ctgaccataa  
 3601 cgtattatac attcaagaaa ggtcaaaac cagatatact agaaaccaat cttttttt  
 3661 taccacctta ctaggtaagg gcctggatc caagaagtga ctgctcatc aatccataa  
 3721 gctatgtaa cagattggag gtagtagcat ttctattaca agtgactaaa agaacagctg  
 3781 ttaccctctg atcgtgcagc agtgcttct gttcctaga atttgcctt gtaagtcta  
 3841 gctcaagttg ggggtgtgtg atagacattt aagaagccat atatctttc agaagtaggt  
 3901 gtgatgtact aaaagttga gacacttct agaagctca ctattaaagt tatgactagt  
 3961 attggatttt tggcatgtct ttgggttca tgttcttaa cccaactgcc tgcagggcct  
 4021 tatggctgtc aggagcagtt ctgggaatt aaagtaatta ctgaagaagt attctagtga  
 4081 gaaaatgaat ttatgactca gaagccccta aagacatggg tactaagcaa caaataaagc  
 4141 agatgtaat taactgtaat ttctcttac agctgttgc agacaaggtc ccaaagacag  
 4201 cagggtgtgc cattttctaa gttaacaaa gatgttcaa ttgtgacagt ttgtgtgt  
 4261 gtgtgtatat atatatttt atgtatgtat atatgtgtt aattttttt taaacagaaa  
 4321 atttctgic tctgagcact ggagagaaaag gatttggta taagggttc tgcttcaca  
 4381 gaattattcc aggtttatg tgcaggtag gaaattact gaattttat ttattgggt  
 4441 tgcctcctc atttgggatt gagccagaat attcaggat acacatatc gaactgtac  
 4501 tctaccattt cggttctatt taaccttct attcagttg aacttgggt taaagttga  
 4561 acctgcaga ttggcacac ttcatggta tgtgtcaga agtgacattt ttctatatg  
 4621 ttgacagggt ggtgactca cagccataa tggcactgg gtcaagtcga tctatggga  
 4681 gaaattgaa gatgagaact tcatcctaaa gcatacgggt cctggcatc tgcctatggc  
 4741 aaatgctgga ccaacacaa atggttccca gttttcctc tgcactgcca agactgagtg  
 4801 gtaagggtac aacatggcac actaaccacc tgactaaatg aaaagttgcc ctggggggaa  
 4861 cggaacaaac actactttc ttcaacctt gctccacag acttttcat ccctaagata  
 4921 ctagaagaag agcatalata aatgacaaat atagccaatg tgatacagaa tgcagatac  
 4981 tatgatagaa acttggccct tagctgggtg gtgaattag gtgctactt ttgagatgg  
 5041 agtttctc tttgtccagg ttggagtga gtggcacaat ctgggtcac tgcaacctc  
 5101 gcctcctggg ttcaagcgt tctctgcct tggcctcctg agtagctgag aatacagatg  
 5161 tgtccagca tgcctggcta atttttga ttttggga gacggggtt catcatgtg  
 5221 gccaagctgg tctgaactc gtgacttaag tgaaccacc tgccttggc ccccaaagt  
 5281 ctgggattc agcatgagc cactgcgcc aaccaattaa gtgctttt ttttttt  
 5341 ctttctcag actggatctc gctttatc cccaggttg agtgagtg tgccatcga  
 5401 gctactgca acctcctccc ggttcaagc aattctct cctcagctc tcaagtagct  
 5461 ggaactacag gcatgcacca cactcccg ctaaatgtg tattattagt agagcgggat  
 5521 ttaccatgt gtccaggctg gtctgaact cctgggtca agtgatctg ctgcctgac  
 5581 cccccgaag tctggggtt acaggcatga gccactgtc ccaccaatt aagtctgct  
 5641 ttatgttac tattaataac atcggttgg ttgggtttt tgttcttg gggttttgt  
 5701 ttgtttgt ttgttttg gggaggggg cgcaattcat tctatagt taactctt  
 5761 ttgagtga gtttctct gtcgccagg ctggagtga gtggcgcat ctggctcac

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5821 tgcaagctcc gcctcccagg ttcacgcat tctcctgcct cagcctccc agtagctggg  
5881 actataggca catgccacca tgcccggcta atttttgta ttttagtag agacaggggt  
5941 tcaccgtgtt agccaggatg gtcctgatct cctgacctcg tgatccgcc gccttggcct  
6001 cccaaagtgc tgggattaca ggcgtgagcc accgcacccg gcctatatgt gtaactctt  
6061 aatggtaatt ggagaatcat gttaatgac atttagtaca aaaggctca gtaaaaaaa  
6121 aaaaaaaaa gctaccttc tctcttgg tcatgacaca tggaggctgc ttgtttggtg  
6181 ttgccagtca taatgattgt tctccttt caaggttga tggcaagcat gtggtgttg  
6241 gcaaagtga agaaggcatg aatatgtgg aggccatgga gcgcttggg tccaggaatg  
6301 gcaagaccag caagaagatc accattgctg actgtggaca actcgaataa gtttgactg  
6361 tgttttatct taaccaccag atcattcct ctgtagctca ggagagcacc cctccacccc  
6421 atttgctgc agtatcctag aatcttgg tctcgtgc agttccctt gggttccatg  
6481 tttccttgt tcctcccat gcctagctgg attgcagagt taagttaatg attatgaaat  
6541 aaaaactaaa taacaattgt cctcgttga gtttaagtgt gatgtaggct ttatttaag  
6601 cagtaatggg ttacttctga aacatcactt gttgcttaa ttctacacag tacttagatt  
6661 tttttactt tccagtccta ggaagtgtca atgtttgtg agtgaatat t

protein sequence for Human cyclophilin gene for cyclophilin:

MVNPTVFFDIAVDGEPLGRVSFELFADKVPKTAENFRALSTGEKGFYKGSFHRIPGFMCQGGDFTRHNGTGKSI  
YGEKFEDENFILKHTGPGILSMANAGPNTNGSQFFICTAKTEWLDGKHVVFQKVKEGMNIVEAMERFGSRNGKTSKKI  
TIADCGQLE

**Figure 12. (Page 12 of 33)**

M12886. Human T-cell rece...[gi:339009]:

Human T-cell receptor active beta-chain mRNA

DNA sequence:

```
1 gtgtgaggcc atcacggaag atgctgctgc ttctgctgct tctggggcta gcaggctccg
61 ggcttggtgc tgtcgtctct caacatccga gctgggttat ctgtaagagt ggaacctctg
121 tgaagatcga gtgccgttcc ctggacttcc aggccacaac tatgttttgg tatcgtcagt
181 tcccgaaaaca gagtctcatg ctgatggcaa ctccaatga gggctccaag gccacatacg
241 agcaaggcgt cgagaaggac aagtttctca tcaacatgc aagcctgacc ttgtccactc
301 tgacagtgcag cagtgcccat cctgaagaca gcagcttcta catctgcagt gctagagagt
361 cgactagcga tcaaaaaaat gagcagttct tcgggccagg gacacggctc accgtgctag
421 aggacctgaa aaacgtgttc ccaccgagg tcgctgtgtt tgagccatca gaagcagaga
481 tctcccacac ccaaaaggcc acactgggtg gcttgccac aggcttctac cccgaccacg
541 tggagctgag ctggtgggtg aatgggaagg aggtgcacag tggggtcagc acagaccgcg
601 agccccctcaa ggagcagccc gccctcaatg actccagata ctgcctgagc agccgcctga
661 gggctctggc caccttctgg cagaaccccc gcaaccactt ccgctgtcaa gtccagttct
721 acgggctctc ggagaatgac gagtggaccc aggatagggc caaacctgtc acccagatcg
781 tcagcgccga ggcctggggt agagcagact gtggcttcac ctccgagtct taccagcaag
841 gggctcgtgc tgccaccatc ctctatgaga tcttgctagg gaaggccacc ttgtatgccg
901 tgctggtcag tgccctcgtg ctgatggcca tggtaagag aaaggattcc agaggctagc
961 tcaaaaacca tccagggtca ttctcatcc taccaggga ttctcctgta cctgctccca
1021 atctgtgttc ctaaaagtga ttctactct gcttctcatc tctacttac atgaatactt
1081 ctctctttt tctgtttccc tgaagattga gctccc
```

protein sequence:

```
MLLLLLLLGLAGSGLGAVVSQHPSWWICKSGTSVKIECRSLDFQATTMFWYRQFPKQSLMLMATSNEGSKATYEQGV
EKDKFLINHASLTLSTLTVTSAHPEDSSFYICSARESTSDPKNEQFFGPGTRLTVLEDLKNVFPPEVAVFEPSEAEISHT
QKATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDQPQLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRCQVQ
FYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESYQQGVLSATILYEILLGKATLYAVLVSAVLVLMAMVKRKDS
RG
```

**Figure 12. (Page 13 of 33)**

M83664. Human MHC class I...[gi:188478]:

Human MHC class II lymphocyte antigen (HLA-DP) beta chain mRNA

DNA sequence:

```
1 agcgagtcct tctttcctg actgcagctc tttcathtt gccatccttc tccagctcca
61 tgatggttct gcaggtttct gcggccccc ggacagtggc tctgacggcg ttactgatgg
121 tgctgtcac atctgtggtc cagggcaggg ccactccaga gaattacgtg taccagggac
181 ggcaggaatg ctacgcgttt aatgggacac agcgcttct ggagagatac atctacaacc
241 gggaggagta cgcgcgttc gacagcgacg tgggggagtt ccgggcggtg acggagctgg
301 ggcggcctgc tgcggagtac tggaaacagc agaaggacat cctggaggag aagcgggcag
361 tgccggacag ggtatgcaga cacaactacg agctggacga ggccgtgacc ctgcagcgcc
421 gagtccagcc taaggatgaac gtttccccct ccaagaaggg gccctgcag caccacaacc
481 tgctgtctg ccacgtgaca gatttctacc caggcagcat tcaagtcga tggttcctga
541 atggacagga ggaacagct ggggtcgtgt ccaccaacct gatccgtaat ggagactgga
601 ccttcagat cctggtgatg ctggaatga ccccccagca gggagacgtc tacatctgcc
661 aagtggagca caccagcctg gacagtctg tcaccgtgga gtggaaggca cagtctgatt
721 ctgccagag taagacattg acgggagctg ggggtctcgt gctggggctc atcatctgtg
781 gagtgggcat ctcatgcac agggaggagca agaaagtca acgaggatct gcataaacag
841 ggttctgac ctaccgaaa agactaatgt gccttagaac aagcatttgc tgtgtttgt
901 taacacctgg ttccaggaca gacctcagc ttccaagag gatactgtg ccaagaagtt
961 gctctgaagt cagtttctat cgttctgctc ttgattcaa agcactgttt ctctactgg
1021 gcctccaacc atgttccctt ctcttagca ccacaaataa tcaaaaccca acataagttg
1081 ttgcttctt taaaaatat gcatcaaac gtctctcatt acttttctt gagggtttta
1141 gtaaacagta ggagttaata aagaagtca ttttggtta cacgtaggaa agaagagaag
1201 catcaaagtg gagatatgtt aactattgta taatgtggcc tgtatacat gacactctc
1261 tgaattgact gtaattcagt gagctgcccc caaatcaagt ttagtgcct catccattta
1321 tgtctcagac cgctattctt aactattcaa tggtagcag actgcaaac tgcctgatag
1381 gacctatatt cccacagcac taattcaaca tatacttac tgagagcatg tttatcatt
1441 accattaaga agttaatga acatcagaat taaaatcat aatataatc taatacatt
1501 t
```

protein sequence:

```
MMVLQVSAAPRTVALTALLMVLTSVVQGRATPENIVYQGRQECYAFNGTQRFLERYIYNREEYARFDSVDVGEFRAV
TELGRPAAEYWNSQKDILEEKRAVPDRVCRHNYELDEAVTLQRRVQPKVNVSPSKKGPLQHHNLLVCHVTDFYPGSI
QVRWFLNGQEETAGVVSTNLIRNGDWTQILVMLEMTQQGDVYICQVEHTSLDSPVTVEWKAQSDSAQSKTLTGA
GGFVLGLIICGVGIFMHRRSKKVQRGSA
```

**Figure 12. (Page 14 of 33)**

D83779. Human mRNA for KI...[gi:1228040]

Human mRNA for KIAA0195 gene, complete cds

```
1  cggacatggc tgcggccccc ggaggagggg acgtgaagtg aggagggggg tgggagggga
61  gaggacgagg gcgaggaaga ccagccccgg ggccccgatg ttgtgactgt gacagactca
121 ctgggggttg tacatgctgg ggaggagcct tccttcagg ggtgaccaca ttcactggg
181 catgcctgca gtactcttgg cccatggacc tgaaggagaa gcacctgggc gagcctccct
241 cagccctggg cctgtccacg cggaaggccc tcagcgtcct gaaggagcag ctggaggcag
301 tgctggaagg acatctcagg gacggaaga agtgtctgac gtggaaggag gtgtggagaa
361 gcagcttctc ccaccacagt aaccgctgct cctgcttcca ctggccgggg gcctactca
421 tgctactggc cgtgctgctg ctgtggggt gctgcggggg acagccagcc gggagccgtg
481 ggggtggggt ggtgaatgcc tcggcctgt tctgttact gcttcaac ctgtgtctca
541 tcgggcggca agaccggctg aagcgtcggg aggtagagcg gaggtgcga gggatcattg
601 accaaatcca agatgccctc agggatggca gggagatcca gtggcccagt gccatgtac
661 cagacctcca catgcctttt gcgccatct ggtccttga ctgggcctac agagacggac
721 acctggtcaa cctgccagtc agcctgctgg ttgaaggaga catcatagct ttgaggcctg
781 gccaggaatc gttgtctct ctgaggggga tcaaggatga cgagcacatc gtctggagc
841 cgggagacct ctccccccc ttctccctc caccctcacc ccggggagaa gtggagagag
901 ggccacagag ccccacagcag caccggcttt tccgtgtcct tgagaccctt gtgattgaca
961 acatcagatg gtgcctggac atggccctgt cccgaccagt cactgccctg gacaatgagc
1021 gggtcacagt gcagtcgggt atgtacact atgtgtgcc cgtgtcctg gccggcttc
1081 tcatcaccaa tgcctgcgc ttcacttca gtgccccggg ggtcacttc tggcagtaca
1141 cctctctcca gctccagggt aatggcgctc tgcctatct cccctgtc tttcagtc
1201 tctgggttct ggcaactgcc tgtggagagg cccgtgtcct ggcccagatg agcaaggcct
1261 caccagctc cctgctggt aagtctcag aggtactct cagcagctat acggaggctg
1321 tctctctca ggaatgctg cgctgcattt ggggccactt cctgagggtg ctgggggga
1381 catcgccaac gctgagccac agtccagcc tctgcacag cctgggtct gtacaggtcc
1441 tgtgtgtgt ggacaacag gggatcctgt catggccaaa tccagccca gagactgtac
1501 tttctctcag cggaagggtg gagccccctc acagcagcca tgaggacct accgatggcc
1561 tatccacccg ctctctgc catcccgagc cccatgaacg agacgccctc ctggttggt
1621 cctgaacaa caccctgcac cttccaatg agcaggagcg tggcgactgg cctggcgagg
1681 ctccaagcc ccccgagccc tatcacacc acaaagcgca tggccgcagc aaacacccat
1741 ctggctcaa cgtgagcttc agcagggaca ccgagggtgg tgaagaagag cccagcaaga
1801 cccagcctgg gatggagagc gacccctacg aagcagagga cttgtgtgt gactaccacc
1861 tggagatgct gagcctgtcc caggaccagc agaaccctc ctgcatccag ttgatgact
1921 ccaactggca gctgcacctc acctccctca aaccctggg cctcaatgtg ctgctgaacc
1981 tgtgtgatgc cagcgtcacc gagcgctgt gccgattctc cgaccacctg tgcaacattg
2041 cctgcaaga gagccacagc gccgtgctgc ccgtccatgt gccctggggc ctctgcgagc
2101 ttgcccgcct cattggcttc actcctggg ccaaggagct ttcaagcag gagaaccatc
2161 tggcgctgta ccgctcccc agtgccgaga caatgaagga gacatcgctg gggcggtct
2221 cctgtgtcac caagcggcgg cctccctca gccacatgat cagcctctc attaaagaca
2281 ccaccaccag cacagagcag atgtgtccc atggaccgc tgatgtgtc ttagaggcct
2341 gcacagactt ctgggacgga gctgacatct acctctctc gggatctgac agaaagaaag
2401 tctgtgactt ctaccagcga gcctgcctgt ctgggtattg ctctgcctc gcctacaagc
2461 ccatgaactg cgccctgtcc tctcagctca atggcaagt catcgagctg gtacaggtgc
2521 ccggccaaag cagcatctc accatgtgcg agctgccag caccatcccc atcaagcaga
2581 acgcccgcg cagcagctgg agcttgacg aaggatcgg ggagggtctg gagaaggaag
2641 atgcatgca ggccctgagc ggccagatct tcatgggcat ggtgtcctc cagtaccagg
2701 cccggttga catcgtgcgc ctcatgtat ggctgtcaa cgctgcac cgtttgtct
2761 acttctctt ggaggatgag ctcaaaagca aggtgttgc agaaaaaatg ggctggaga
```



**Figure 12. (Page 15 of 33)**

2821 caggctggaa ctgccacatc tcctcacac ccaatggtga catgcctggc tccgagatcc  
2881 cccctccag cccagccac gcaggctccc tgcagatga cctgaatcag gtgtcccgag  
2941 atgatgcaga agggctctc ctcatggagg aggagggcca ctggacctc atcagctcc  
3001 agcctacgga cagcgacatc cccagcttc tggaggactc caaccgggcc aagctgcccc  
3061 ggggtatcca ccaagtgcgg cccacctgc agaactga caacgtgccc ctgctagtgc  
3121 ccttttcac cgactgcacc ccagagacca tgtgtgagat gataaagatc atgcaagagt  
3181 acggggaggt gacctgctgc ctggcagct ctgccaacct gcggaacagc tgcctctcc  
3241 tccagagcga catcagcatt gccctggatc ccctgtacc atcccgtgc tctgggaga  
3301 ccttggtcta cgccaccagc atcagcatgg cccaggcctc ggatggcctt tctccctgc  
3361 agctgtcagg gcagctcaac agcctgccct gttccctgac ctttgcag gagagacca  
3421 tcagcatcat ccggtctatc gaacaggctc ggcatgccac ctatggcatc cgtaagtgt  
3481 tctcttctc gctgcagtgc cagctgactc ttgtgtcat ccagttcctt tcttgctgg  
3541 tccagctgcc gccactctg agtaccaccg acatctgtg gctgtctgc tttgtacc  
3601 ctctgtcag catctctctg ctggggaagc ccccatag ctccatcatg tctatggaa  
3661 cggggaaaaa cctccagtc attccaaga agaccagca ctactctg ctctgtcc  
3721 tgctcaagt cagctcacc atcagctct gccatctg cttggctc acactgcaga  
3781 gcttctgtga cagctccgg gaccgcaacc tcaccaactg ctctccgtc atgctgcca  
3841 gcaacgacga cagggtcca gccgtgttg aggacttgc caatggactg ctgtcgctc  
3901 agaagctcac ggccgccctg attgtctgc acactgtct cattccatc acccatgtc  
3961 atcgaccaa gccctgttg agaaagagcc cctgaccaa cctctgttg gccgtgacg  
4021 tgcctgtgt gctgtgggt cagggtgtc agacggtgt ggacctgcag ctgtggacac  
4081 acagggacag ccacgtccac ttggcctgg aggacgtgc cctgtgaca tggctctgg  
4141 gctgcctgc cctgtcctt gtgtgtgtga ccaatgagat cgtgaagcta catgagattc  
4201 ggttccgagt ccgtaccag aagcgacaga agctgcagt tgaactaag ctgggcatga  
4261 acttccctt ctgagccact ggctgtgtg gctgtagt ccccgctcc tgggctaaa  
4321 gccagacca ttctgaaca ggggagttg tatcatgaat gtctcaggt ttgtctctg  
4381 accgtggca ctggaaacc agtccccgt gtcagaccc gctgtctcc tgagccctg  
4441 ggctactgt ggaggagct acggcctgg ccctggcca gtcctggctc tccctgggc  
4501 ctaccaggg acactctga atgtatggc tcaggcgctc cctagagggg ccctaaacc  
4561 cctaccctg gagctacccc cttaggat ccctgcccc ctggagatc cctgcccc  
4621 cagtgcctt gctgtgggt ccctggacac gccctgaag ccaacctct ttggaggagc  
4681 aacagcagca gcctggccg acgctcaa ctccaaggc tgccgtggag ggcaggggg  
4741 tggctctgc ctggtgtg ccccgagtc ctccctccc tccctctgt gggagctc  
4801 ccgctgaac ctgaagatg agcagggccc ccgtctgc ctggagctc ttcctgtcc  
4861 tggctcaagc tggctgctg tagtcttg ggaatctgc ccaggtctc tcagctctg  
4921 cccagttct gggagaagt tctactgtg tatatttt actggaaatg agcctttag  
4981 gaatgaatg agactggtt gtattaaaat gtgtcaattg ct

**Figure 12. (Page 16 of 33)**

Protein sequence of Human KIAA0195

MDLKEKHLGEPPSALGLSTRKALSVLKEQLEAVLEGHLRERKKC  
LTWKEVWRSSFLHHSNRCSCFHWPGASLMLLAVLLLLGCCGGQPAGSRGVGLVNASAL  
FLLLLLNLVLIGRQDRLKRREVERRLRGIIDQIQDALRDGREIQWPSAMYPDLMHPFA  
PSWSLHWAYRDGHLVNLVPVLLVEGDIIALRPGQESFASLRGIKDDHIVLEPGDLFP  
PFSPPSPRGEVERGPQSPQQHRLFRVLETPVIDNIRWCLDMALSRPVTALDNERFTV  
QSVMLHYAVPVVLGFLITNALRFIFSAPGVTSWQYTLLQLQVNGVLPILPLLFPVLW  
VLATACGEARVLAQMSKASPSSLLAKFSEDTLSSYTEAVSSQEMLRCIWGHFLRVLGG  
TSPTLSHSSSLLHSLGSVTVLCCVDKQGILSWPNPSPETVLFFSGKVEPPHSSHEDLT  
DGLSTRSFCHPEPHERDALLAGSLNNTLHLSNEQERGDWPGEAPKPPEPYSHHKAHGR  
SKHPSGSNVFSRDTEGGESEPSKTQPGMESDPYEAEDFVCDYHLEMLSLSQDQQNPS  
CIQFDDSNWQLHLTSLKPLGLNVLLNLCDAVTERLCRFSDHLCNIALQESHSAVLPV  
HVPWGLCELARLIGFTPGAKELFKQENHLALYRLPSAETMKETSLGRLSCVTKRRPPL  
SHMISLFIKDTTSTEQMLSHGTADVLEACTDFWDGADIYPLSGSDRKKVLDIFYQRA  
CLSGYCSAFAYKPMNCALSSQLNGKCIELVQVPGQSSIFTMCELPSTIPIKQNARRSS  
WSSDEGIGEVLEKEDCMQALSGQIFMGMVSSQYQARLDIVRLIDGLVNACIRFVYFSL  
EDELKSKVFAEKMGLTGWNCHISLTPNGDMPGSEIPPSSPSHAGSLHDDLNQVSRDD  
AEGLLLMEEEGHSDLISFQPTDSDIPSFLEDSNRAKLPRGIHQVRPHLQNDNVPLL  
PLFTDCTPETMCEMIKIMQEYGEVTCCLGSSANLRNSCLFLQSDISIALDPLYPSRCS  
WETFGYATSI SMAQASDGLSPLQLSGQLNSLPCSLTFRQEETISIIRLIEQARHATYG  
IRKCFLLQCQLTLVVIQFLSCLVQLPPLLSTTDILWLSCFCYPLLSISLLGKPPHS  
SIMSMATGKNLQSIPKKTQHYFLLCFLLKFSLTISSCLICFGFTLQSFCDSSRDRNLT  
NCSSVMLPSNDDRAPAWFEDFANGLLSAQKLTAALIVLHTVFISITHVHRTKPLWRKS  
PLTNLWWAVTVPVVLLGQVVQTAVDLQLWTHRDSHVHFGLEDVPLLTWLLGCLSLVLV  
VVTNEIVKLHEIRVRVRYQKRQKLQFETKLG MNSPF

**Figure 12. (Page 17 of 33)****L36719. Homo sapiens MAP ...[gi:685173]****Homo sapiens MAP kinase kinase 3 (MKK3) mRNA, complete cds**

```

1  tggctggcaa tggccttgct gacctgagc cgggcccacg tggggacctt tggagcacag
61  cctacgatcc tggtgcaagg ccggtggatg cagaggccag tccatatacc acccaggcct
121  gcgaggagcg tggccccac ccatccagcc catatgtgca agtgcccttg acagagaggc
181  tggtcataac catggtgacc atttatgggc cacaacaggt ccccatctgc gcagtgaacc
241  ctgtgctgag caccttgacg acgtgatctt gcttctctct gcagcactgt gcggggcagg
301  aaaatccaag aggaagaagg atctacggat atcctgcatg tccaagccac ccgcacccaa
361  cccacacccc ccccggaacc tggactcccg gaccttcac accattggag acagaaactt
421  tgagggtggag gctgatgact tggtgacat ctcaaacctg ggccgtggag cctatggggt
481  ggtagagaag gtgcggcacg ccagagcgg caccatcatg gccgtgaagc ggatccgggc
541  caccgtgaac tcacaggagc agaagcggct gctcatggac ctggacatca acatgcgcac
601  ggtcgactgt ttctacacgt tcacctta cggggcacta tcagagagg gagacgtgtg
661  gatctgcatg gagctcatg acacatcct ggacaagtc taccggaagg tctggataa
721  aaacatgaca attccagagg acatccttg ggagattgct gtgtctatcg tgcgggccct
781  ggagcatctg cacagcaagc tgtcgggtgat ccacagagat gtgaagccct ccaatgtcct
841  tatcaacaag gagggccatg tgaagatgtg tgactttggc atcagtggct acttggtgga
901  ctctgtggcc aagacgatgg atgccggctg caagccctac atggcccctg agaggatcaa
961  ccagagctg aaccagaagg gctacaatgt caagtccgac gtctggagcc tgggcatcac
1021 catgattgag atggccatcc tgcggtccc ttacgagtcc tgggggaccc cgtccagca
1081 gctgaagcag gtggtggagg agccgtcccc ccagctccca gccgaccgtt tctccccga
1141 gttgtggag ttactgtct agtgccctgag gaagaacccc gcagagcgta tgagctacct
1201 ggagctgatg gagcaccctt tctcacctt gcacaaaacc aagaagacgg acattgtctg
1261 ctctgtgaag aagatcctgg gagaagactc ataggggctg ggccctggac ccactccgg
1321 cctccagag cccacagcc ccatctgcgg gggcagtgt caccacacc ataagctact
1381 gccatcctgg ccaggggcat ctgggaggaa ccgagggggc tgctcccacc tggctctgtg
1441 gcgagccatt tgtcccaagt gccaaagaag cagaccattg gggctcccag ccaggccctt
1501 gtgcggccca ccagtgcctc tcctgtctgc tcctaggacc cgtctccagc tctgagatc
1561 ctggactgag ggggcctgga tgcccctgt ggatgtctgt gccctgcac agcaggctgc
1621 cagtgcctgg gtggatgggc caccgccttg ccagcctgg atgccatcca agttgtatat
1681 tttttaatc tctgactga atggacttg cacactttg cccaggggtg ccacacctt
1741 atccggcctt tggtgcgggg tacacaagag gggatgagtt gtgtgaatac cccaagactc
1801 ccatgaggga gatgcatga gccgcccaag gcctcccct ggactggca aacagggcct
1861 ctgcggagca cactggctca ccagtcctg ccgccaccg ttatcgggtg cattcacctt
1921 tcgtgtttt tttaatttat cctctgtga tttttctt tgctttatg gtttgcttg
1981 ttttcttg atggtttga gctgatcgt tctccccac ccctagggg

```

**Protein sequence of Homo sapiens MAP kinase kinase 3 (MKK3)**

```

MSKPPAPNPPTPRNLDSTRTITIGDRNFEVEADDLVTISELGRG
AYGVVEKVRHAQSGTIMAVKRIRATVNSQEQKRLMDLDINMRTVDCFYTVTFYGALF
REGDVWICMELMDTSLDKFYRKVLDKNMTIPEDILGEIAVSIVRALEHLHSLSVIHR
DVKPSNVLINKEGHVKMCDFGISGYLVDSVAKTMDAGCKPYMAPERINPELNQKGYNV
KSDVWSLGITMIEMAILRFPYESWGTPFQQLKQVVEEPSQLPADRFSPFVDFTAQC
LRKNPAERMSYLELMEHPFFTLHKTKKTDIAAFVKILGEDS

```

**Figure 12. (Page 18 of 33)****U47634. Human beta-tubuli...[gi:1297273]****Human beta-tubulin class III isotype (beta-3) mRNA, complete cds**

```

1 atgctgggaga tcgtgcacat ccaggccggc cagtgcggca accagatcgg ggccaagttc
61 tgggaagtca tcagtgatga gcatggcatc gaccccgagc gcaactacgt gggcgactcg
121 gacttcgagc tggagcggat cagcgtctac tacaacgagg cctcttctca caagtacgtg
181 cctcgagcca ttctggtgga cctggaaccc ggaaccatgg acagtgtccg ctacggggcc
241 ttggacatc tcttcaggcc tgacaatttc atcttgggc agagtggggc cggcaacaac
301 tgggccaagg gtcactacac ggagggggcg gagctggtgg attcggctct gtagtggtg
361 cggaaggagt gtgaaaactg cgactgcctg cagggcttcc agctgacca ctgcctggg
421 ggggggacgg gctccggcat gggcacgtg ctatcagca aggtgcgtga ggagtatccc
481 gaccgcatca tgaacacctt cagcgtcgtg cctcaccca aggtgtcaga cacggtggtg
541 gaaccctaca acgccacgct glccatccac cagctggtgg aaaacacgga tgaacctac
601 tgcctgaga acgaggcgct ctacgacatc tgcttcgca cctcaagct ggccacgccc
661 acctacgggg acctcaacca cctggtatcg gccaccatga gcggagtcac cactccttg
721 cgcttccgg gccagctcaa cgctgacctg cgcaagctgg ccgtcaacat ggtgcccttc
781 ccgcgcctgc acttcttcat gcccggttc gcccccctca ccaggcgggg cagccagcag
841 taccgggccc tgacctgcc cgagctcacc cagcagatgt tcgatgcaa gaacatgatg
901 gccgcctgag acccgcgcca cggccgctac ctgacggtgg ccaccgtgtt ccggggccgc
961 atgtcatga aggaggtgga cgagcagatg ctggccatcc agagcaagaa cagcagctac
1021 ttctggagt ggatcccaa caactgaag gtggcgtgt gtgacatccc gccccgaggc
1081 ctcaagatgt cctcacctt catcggaac agcacggcca tccaggagct gttcaagcgc
1141 atctccgagc agttcacggc catgttccgg cgcaaggcct tctgcatg gtacacgggc
1201 gagggcatgg acgagatgga gttcacggag gccgagagca acatgaacga cctggtgtcc
1261 gattaccagc agtaccagga cgccacggcc gaggaagagg gcgagatgta cgaagacgac
1321 gagggaggat cggaggccca gggcccaag tgaactgct cgcagctgga gtgagaggca
1381 ggtggcgccc ggggccaag ccagcagtg ctacaccccc ggagccatct tgctccgac
1441 accctgctt cccatcgcc ctagggtcc ctgcccgc tctgcagta ttatggcct
1501 cgtctcccc cactaggcc acgtgtgagc tgctcctgc tctgttat tgacgtcca
1561 ggcctgacgt ttacgggtt tgtttttac tggtttgt ttatatttc ggggatact
1621 aataaatcta ttgctgtcag ataccctt

```

**Protein sequence of Human beta-tubulin class III isotype (beta-3)**

```

MREIVHIQAGQCGNQIGAKFWEVISDEHGDPSGNYVGSDSLQL
ERISVYYNEASSHKYVPRAILVDLEPGTMDSVRSGAFGHLFRPDNFIQSGAGNNWA
KGYHTEGAELVDSVLDVVRKECENCDCLOQFQLTHSLGGGTGSGMGTLLISKVREEYP
DRIMNTFSVVPSPKVS DTVVEPYNATLSIHLQVENTDETYCIDNEALYDICFRTLKLA
TPTYGDLNHLVSATMSGVTTSLRFPGLNADLRKLAVNMVFPRLHFFMPGFAPLTRR
GSQQYRALTVPELTQQMFDANKMMAACDPRHGRYLT VATVFRGRMSMKEVDEQMLAIQ
SKNSSYFVEWIPNNVKVAVCDIPPRGLKMSSTFIGNSTAIQELFKRISEQFTAMFRRK
AFLHWYTGEGMDEMEFTEAESNMNDLVSEYQQYQDATAEEEGEMYEDDEESEAQGP

```

**Figure 12. (Page 19 of 33)**M19267. Human tropomyosin...[gi:339943]

Human tropomyosin mRNA, complete cds

```

1  cagaatctcc ggcagtttt gtacctcaag aagtaagtgg aacaccttc cctgtcatag
61  ttatttcat ccagacatct ggtggaagca tcagattcct tacagatata agagagggcat
121 catttaaaag gtagaacagg atcgacaaac aaggatttat gtcaggatct ctacagcctct
181 gtgtaccga gggcatttct aacagtcttc ttactacggc ctccgccgac cgcgcgctcg
241 ccccgccgct cctgtctcag cccaggggcc cctcgccgcc gccaccatgg acgccatcaa
301 gaagaagatg cagatgctga agctcgacaa ggagaacgcc ttggatcgag ctgagcaggc
361 ggaggccgac aagaaggcgg cggaagacag gagcaagcag ctggaagatg agctggtgtc
421 actgcaaaag aaactcaagg gcaccgaaga tgaactggac aaatactctg aggctctcaa
481 agatgcccgag gagaagctgg agctggcaga gaaaaaggcc accgatgctg aagccgacgt
541 agcttctctg aacagacgca tccagctggt tgaggaagag ttggatcgtg cccaggagcg
601 tctggcaaca gcttgcaga agctggagga agctgagaag gcagcagatg agagtgagag
661 aggcataaaa gtcattgaga gtcgagccca aaaagatgaa gaaaaaatgg aaattcagga
721 gatccaaactg aaagaggcaa agcacattgc tgaagatgcc gaccgcaa atgaagaggt
781 ggcccgtaa gctgtcatca ttgagagcga cctggaacgt gcagaggagc gggctgagct
841 ctgagaaggc caagtcggac agctggaaga acaattaaga ataatggatc agacctgaa
901 agcattaatg gctgcagagg ataagtactc gcagaaggaa gacagatatg aggaagagat
961 caaggtcctt tccgacaagc tgaaggagc tgagactcgg gctgagttg cggagaggtc
1021 agtaactaaa ttggagaaaa gcattgatga cttagaagag aaagtggctc atgccaaga
1081 agaaaacctt agtatgcac agatgctgga tcagacttta ctggagttaa acaacatgtg
1141 aaaacctct tagctgcgac cacattctt cattttgtt tgtttgtt tgttttaaa
1201 cacctgcta cccctaaat gcaatttat tactttacc actgtcacag aaacatccac
1261 aagataccag ctaggtcagg gggtagggaa aacacatata aaaagcaagc ccatgtcagg
1321 gcgatcctgt ttcaaatgtg ccatttccc ggttgatgct gccacattt gtagagagtt
1381 tagcaacaca gtgtgcttag tcagcgtagg aatcctcact aaagcaggag aagttccatt
1441 caaagtgcc aatgatagat caacaaggaa ggtaatgtt ggaaacacaa tcagggtgtg
1501 attggtgcta cttgaacaa aaggcccc tgtggtctt tgttaacat tgtacaatgt
1561 agaactctgt ccaacactaa ttattttgt ctgagtttt actacaagat gagactatgg
1621 atcccgcatg cct

```

Protein sequence of Human tropomyosin

```

MDAIKKKMQMLKLDKENALDRAEQAEADKKAEDRSKQLEDELV
SLQKKLKGTEDELDKYSEALKDAQEKLELAEEKATDAEADVASLNRRRIQLVEEELDRA
QERLATALQKLEEAKEADESERGMKVIESRAQKDEEKMEIQEIQLKEAKHIAEDADR
KYEEVARKLVIESDLERAEEAELSEGQVRQLEEQLRIMDQTLKALMAAEDKYSQKE
DRYEEEEIKVLSDKLKEAETRAEFAERSVTKLEKSIDDLKVAHAKEENLSMHQMLDQ
TLELNNM

```

**Figure 12. (Page 20 of 33)**S78798. 1-phosphatidylinositol...[gi:1042033]

1-phosphatidylinositol-4-phosphate 5-kinase isoform C [human, peripheral blood leukocytes, mRNA, 1835 nt]

```

1 ttacatttta tacttccggc tcgaatattg tgtggaattg tgancggata acaatttcac
61 acaggaaaca nctatgacct tgattacgcc aagctcgaaa ttaacctca cttaaaggaa
121 caaaagctgg agctcgcgcg cctgcaggtc gacactagt gatccaaaga attcggcacg
181 aggcgacggg cggagcggag cgcggcgcgc cggggccgcc gccgggggga tcggctgcct
241 ccccgggccg ggtgtagaga gggcggttcc cggcctcgg gagcacggcg gtggagggga
301 cataggaggc ggccatggcg accccggca acctagggtc ctccgtcctg gcgagcaaga
361 ccaagaccaa gaagaagcac ttcgtagcgc agaaagtga gctgttcgg gccagcgacc
421 cgctgctcag cgtcctcatg tggggggtaa accactcgt caatgaactg agccatgttc
481 aaatccctgt taigtgatg ccagatgact tcaaagccta tcaaaaata aaggtggaca
541 atcacctttt taacaaagaa aacatgccga gccattcaa gtttaaggaa tactgcccga
601 tggcttccg taactcggg aagaggttg gaattgatg tcaagattc cagaattccc
661 tgaccaggag cgcacccctc ccaacgact ccaggcccg cagtggagct cgttttaca
721 ctccctacga caaaagatac atgatcaaga ctattaccag tgaagacgtg gccgaaatgc
781 acaacatct gaagaaatac caccagtaca tagtggatg tcatgggatc accctcttc
841 cccacttgtt gggcatgtac cggctaatg ttgatggag tgaatatat gtgatagta
901 caagaaatgt attcagccac cgtttgtctg tcataggaa atacgacta aagggtcta
961 cagtggctag agaagctagt gacaaagaaa agccaaaga actgccaact ctgaaagata
1021 atgatttcat taatgaggc caaaagattt atattgatg caacagcaag aaggtcttc
1081 tggaaaaact aaaaaaggat gttgagttc tggccagct gaagctcatg gactacagt
1141 tgctgggtgg aattcatgat gtggagagag ccgaacagga ggaagtgag tgtgaggaga
1201 acgatgggga ggaggaggc gagagcgtg gcacccaccc ggtgggaacc ccccgagata
1261 gccccgggaa tactatgaac agtcaccac ccttggtcc cggggagttc gagccgaaca
1321 tcgacgtcta tggaattaag tgccatgaaa actcgcctag gaaggaggtg tacttcatgg
1381 caattattga catccttact cattatgatg caaaaaagaa agctgcccat gctcaaaaa
1441 ctgttaaaca tggcgtggc gcggagatct ccaccgtga cccagaacag tattcaaagc
1501 gctttttgga cttattggc cacatctga cgtaacctcc tgcgcayctc ggacagcatg
1561 aacattggat ggacagaggt ggctcggg taggaaaaat gaaaaccaa ctcagtgaag
1621 tactcatct gcaggaagca aacctcctg ttacatctt caggccaaga tgactgatt
1681 gggggctact cgctttacag ctacctgatt tcccagcat cgttctagct atttctgact
1741 ttgtgtatat gtgtgtgtgt gtgtgtggg ggggggtgag tgtgtccc cggtgtgcat
1801 taaagcataa attaattaaa cagccactc ggtca

```

Protein sequence of 1-phosphatidylinositol-4-phosphate 5-kinase isoform C

```

MATPGNLGSSVLASKTKTKKKHFVAQKVLFRA SDPLLSVLMWG
VNHSINELSHVQIPVMLMPDDFKAYSKIKVDNHLFNKENMP SHFKFKEYCPMVFRNCG
KRFGIDVQDFQNSLTRSAPLPNDSQARSGARFHTSYDKRYMIKTITSEDVAEMHNILK
KYHQYIVECHGITLLPHLLGMYRLNVDGVEIYVIVTRNVFSHRLSVYRKYDLKGSTVA
READSKEKAKELPTLKDNDFINEGQKIYIDDNSKKVFLEKLKKDVEFLAQLKLM DYSL
LVGIH DVERAEQEEVECEENDGEEGESD GTHPVGTPPDSPGNTLNSSPPLAPGEFEP
NIDVYG ICHENS PRKEVYFMAIIDILTHYDAKKKAAHAAKTVKHGAGAEISTVNPEQ
YSKRFLDFIGHILT

```

**Human MLC1emb gene for embryonic myosin alkaline light chain, promoter and exon 1**

Protein sequence of Human MLC1emb gene for embryonic myosin alkaline light chain, promoter and exon 1  
MAPKKPEPKKEAAKPAPAPAPAPAPAPAPEAPKEPAFDPKSV  
KIDFTADQIEEFKEAFSLFDRTPTGEMKITYGQCGDVLRLALGQNPTNAEVLRLVLGKPK  
PEEMNVKMLDFETFLPIQLHISRNEKQGTYEDFVEGLRVFDKESNGLTVMGAELRHVLA  
TLGKMTAEAEVEQLLAGQEDANGCINYEAFHGHIMSG

**Figure 12. (Page 22 of 33)**X90999. H.sapiens mRNA fo...[gi:1237212]

H.sapiens mRNA for Glyoxalase II

```
1 gatttgcgga agaacctgac cgtggacgag ggcaccatga aggtagaggt gctgcctgcc
61 ctgaccgaca actacatgta cctggtcatt gatgatgaga ccaaggaggc tgccattgtg
121 gatccggtgc agcccagaa ggtcgtggac gcggcgagaa agcacggggt gaaactgacc
181 acagtgtca ccaccacca ccactgggac catgctggcg ggaatgagaa actggtaag
241 ctggagtgg gactgaaggt gtacgggggt gacgaccgta tcggggccct gactcacaag
301 atcactcacc tgtccacact gcagggtggg tctctgaacg tcaagtgcct ggcgaccccc
361 tgccacactt caggacacat ttgttacttc gtgagcaagc ccggagggtc ggagccccct
421 gccgtgttca caggtagacac ctgtttgtg gctggctgcg ggaagttcta tgaagggact
481 gcggatgaga tgtgtaaagc tctgctggag gtcttgggcc ggctcccccc ggacacaaga
541 gtctactgtg gccacgagta caccatcaac aacctcaagt ttgcacgcca cgtggagccc
601 ggcaatgccg ccatccggga gaagctggcc tggccaagg agaagtacag catcggggag
661 cccacagtgc catccacctt ggcagaggag ttacctaca accccttcat gagagtgagg
721 gagaagacgg tgcagcagca cgcaggtgag acggacccgg tgaccacat gcgggccgtg
781 cgcagggaga aggaccagtt caagatgcc cgggactgag gccgccctgc acctcagcg
841 gatttggga ttaggtctt ttagtaact ggcttctg ctgtccgtg cgggaaattc
901 agtctgatt taacctaat ttacagccc ttggctgtg ttatcgga ttctaatga
961 tattataag agaagtttaa caagtattt ttccataaa aaaaaaaaaa a
```

Protein sequence of H.sapiens mRNA for Glyoxalase II

```
MKVEVLPALTDNYMYLVIDDETKEAAIVDPVQPQKVVDAAARKHG
VKLTTVLTTTHHHWDHAGGNEKLVKLESGLKVYGGDDRIGALHKITHLSTLQVGSINV
KCLATPCHTSGHICYFVSKPGGSEPPAVFTGDTLFFVAGCGKFYEGTADCKALLEVL
GRLPPDTRVYCGHEYTINNLFARHVEPGNAAIKELAWAKEKYSIGEPTVPSTLAE
FTYNPFMRVREKTVQQHAGETDPVTTMRAVRREKDKQKMPRD
```



**Figure 12. (Page 23 of 33)****AF027515. Homo sapiens tran...[gi:2772909]****Homo sapiens trans-golgi network glycoprotein 48 (TGN) mRNA**

```

1 agagggggccc gcgcgcgga tctcgcgaga gcattagagg gcggaagcgc tatccgagca
61 ggatgcggtt cgtggtgcc ttggtcctcc tgaacgtcgc agcggcgga gccgtgccgc
121 tcttgccac cgaagcgtc aagcaagaag aagctggagt acggccttct gcaggaaacg
181 tctccacca cccagcttg agccaacggc ctggaggctc taccaagtcg catccggagc
241 cgcagactcc aaaagacagc cctagcaagt cgagtgcgga ggcgcagacc ccagaagaca
301 cccccaacaa gtcgggtggg gaggcaaaga ccctaaaaga cagctccaac aagtcgggtg
361 cggaggcaca gaccccaaaa ggcagcacta gcaagtcggg ttcggaggcg cagaccacaa
421 aagacagcac tagtaagtcg catccggagc tgcagactcc aaaagacagc actggcaaat
481 cgggtgcgga ggcgcagacc ccagaagaca gcccacacag gtcgggtgcg gagccaaaga
541 cccaaaaaga cagccctagc aagtcagggt cggaggcgca gaccacaaaa gatgtcccta
601 ataagtcggg tgcggcggc cagaccccaa aagacggctc cagcaagtcg ggtgcggagg
661 atcagacccc aaaagacgtc ctaacaagt cgggtgcgga gaagcagact ccaaagacg
721 gctctaaca gtccggtgca gaggagcagg gcccaataga cgggccacg aagtcgggtg
781 cggaggagca gacctcaaaa gacagcccta acaagggtgt tccagagcag ccttcccgga
841 aagaccattc caagccatc tccaaccctt ctgatacaa ggagctcccc aaggctgaca
901 caaaccagct tgctgacaaa ggggaagctt ctctcatgc ttcaaaaacc gaatctggg
961 aggaaactga cctcattct ccccgagg aggaagtaa gtctcagag cctactgagg
1021 atgtggggcc caaagaggct gaagatgatg atacaggacc cgaggagggc tcaccgcca
1081 aagaagagaa agaaaagatg tccggttctg cctccagtga gaaccgtgaa gggacactt
1141 cggattccac gggtagcgag aaggatgacc ttatccgaa cggttctgga aatggcagcg
1201 cggagagcag ccactcttt gcatactgg tgactgcagc cattcttg gctgtcctt
1261 atatgcctc tcacaacaag cgaagatca ttgctttgt cctggaagga aaaagatcta
1321 aagtcacccg gcggccaag gccagtgact accaacgtt ggaccagaag atctttctc
1381 cccaagatcc taacagaatg gtatattct ctggaaaaag atgaacgtc ccaatggatt
1441 gtgctgctc ctgttcagct ttgattttt tglcctgag aacctgtcc tcctgctga
1501 tttgttcta aatcaaaaaga aatgaagaaa aaagtactgt gacctgagag acacctctc
1561 ctagaattta gtggcgggtc tgggtggca gaggtagggg gctgcttgg gcttgcacc
1621 tgcacttgg tgacattgt ctctgtgt cctttattt atgctggtg ctccatccg
1681 ttctcctcg gggtagtg aggggtatat ggaaacacg ctagaccaa agggagatcc
1741 cagcctgggc agcctgcgt gctgaccacc ctccctggg cccgggctct gtaggaaagt
1801 tggctctga ctgtggcatt gcacttgca ctgttctct ctgcagacct aggggaaaac
1861 tgcagggtga agtctttt tactaaggcc tctactttg ggggggatgt gccctacaga
1921 agacatagaa gatggggaaa tgccaatggg caaagagcta cttgaatac ataattctc
1981 tcaaagactc cagcagaaa cctaaacagc aggttaaaaa aaaagatgt ttttgggtg
2041 caagtctaac ctgtctagca tgagatctc ttgatttct gattattta ttagcttga
2101 gacaaagtga atcaactcc acttagtgt accgagcata aaacagaact tgggcttct
2161 ggcagtgagg ccactgtccc atcacagatt ttaaaaataa atatgattg aagtagtgt
2221 atcttcaca caa

```

Protein sequence of Homo sapiens trans-golgi network glycoprotein 48 (TGN)

```

MRFVVALVLLNVAAAGAVPLLATESVKQEEAGVRPSAGNVSTHP
SLSQRPGGSTKSHPEPQTPKDSKSSAEAQTPEDTPNKSNGEAKTLKDSSNKSAGAE
QTPKSGTSKSGSEAAQTTKDSTKSHPELQTPKDSTGKSGAEAQTPEDSPNRSGAEPK
TKDSTKSGSEAAQTTKDVPNKSAGADGQTPKDSSKSGAEDQTPKDVPNKSAGAEKQTPK
DGSNKSAGAEQGPIDGPKSGAEQTSKDSNPKVVPQPSRKDHSKPISNPSDNKELP
KADTNQLADKGLSPHAFKTESGEETDLISPPQEEVKSSEPTEDVGPKEAEDDDTGPE
EGSPPKKEEKEKMSGSSASSENREGTLDSTGSEKDDLYPNGSGNGSAESSHFFAYLVTA
AILVAVLYIAHHNKRKIIAFVLEGRKSKVTRRPKASDYQRLDQKIFSPSPNRMVYSS
GKR

```

**Figure 12. (Page 24 of 33)**

AJ223352. Homo sapiens mRNA...[gi:3255996]

**Homo sapiens mRNA for for histone H2B**

```
1 gcggttcgcc ttcaacatgc cggaaccagc gaagtcgct cccgcgccc agaagggctc
61 gaagaaagcc gtgactaagg cgcagaagaa ggacggtaag aagcgcaagc gcagccgcaa
121 ggagagctac tccgtatacg tgtacaaggt gctgaagcag gtccacccc acaccggcat
181 ctctctaag gccatgggaa tcatgaactc ctctgtaac gacatctcg aacgcatcgc
241 gggtagggct tccgcctgg cgcattacaa caagcgctcg accatcacct ccaggagat
301 ccagacggcc gtgcgctgc tctgcccgg ggagttggcc aagcacgccg tgtccgaggg
361 caccaaggcc gtcaccaagt acaccagcg taagtaaact tgccaaggag ggactttctc
421 tggaaattcc tgatatgacc aagaaagctt cttatcaaaa gaagcacaat tgccttcgg
481 tacctcatta tctactgcag aaaagaagac gagaatgcaa ccatacctag atggactttt
541 ccacaagcta aagctggcct ctgatctca ttcagattcc aaagagaatc atttacaagt
601 taatttctgt ctcttggtc cattcctct ctttaataat catttactgt tctcaaaga
661 attgtttaca ttacccatct cctctttgc tctgagaaag agtatataag ctctgtacc
721 ccactggggg gtgggggtaa tatctgtgg tctcagccc tgtacctaa taaatttga
781 tgccttttt tttaaaaaa aaaaaaaaa aaaaaaaaa aaaaaaaaa
```

**Protein sequence of human histone H2B**

```
MPEPAKSAPAPKKGSKKAVTKAQKKDGKKRKRKSRKESYSVYVYK
VLKQVHPDTGISSKAMGIMNSFVNDIFERIAGEASRLAHYNKRSTITSREIQTAVRL
LPGELAKHAVSEGTKAVTKYTSK
```

**Figure 12. (Page 25 of 33)****L42542. Human RLIP76 prot...[gi:974142]****Human RLIP76 protein mRNA, complete cds**

```

1 agtctggttt aactggttgg aacgactaaa gcacgtggc gcaaggaaag ctctcaact
61 cgggagctga ggcgcaggct ggccagagcg tggagaggaa agccctttcc atcctcaagg
121 ccgttgacag agatgccgc gagccacct cgccagcacc acaccgggt gtaatggata
181 ggtaacagag aagacctcgt ccttcctag tcagggcac agcatgactg agtgcttct
241 gccccccacc agcagcccca gtgaacaccg cagggtggag catggcagcg ggcttaccg
301 gacccccagc tctgaagaga tcagccctac taagtttct ggattgtacc gcactggcga
361 gccctcacct cccatgaca tcttcatga gcctcctgat gtagtgtctg atgatgagaa
421 agatcatggg aagaaaaaag ggaaatttaa gaaaaaggaa aagaggactg aaggctatgc
481 agcctttcag gaagatagct ctggagatga ggcagaaagt ccttctaaaa tgaagggtc
541 caagggaatc catgttttca agaagcccag ctttctaaa aagaaggaaa aggatttaa
601 aataaaagag aaacccaaag aagaaaagca taaagaagaa aagcacaag aagaaaaaca
661 taaagagaag aagtcaaaag actgacagc agctgatgtt gtaaacagt ggaaggaaaa
721 gaagaaaaag aaaaagccaa ttcaggagcc agaggtcct cagattgatg ttccaaatct
781 caaacccatt ttggaattc ctttggtga tgcagtagag aggaccatga tgtatgatg
841 cattcggtc cagccgtt tccgtgaatg tatagattac gtagagaagt atggcatgaa
901 gtgtgaaggc atctacagag tatcaggaat taaatcaaag gtggatgagc taaaagcagc
961 ctatgaccgg gaggagtcta caaactgga agactatgag cctaacactg tagccagttt
1021 gctgaagcag tatttgcgag acctccaga gaatttgctt accaaagagc ttatgccag
1081 atttgaagag gctgtggga ggaccacgga gactgagaaa gtgcaggaat tccagcggtt
1141 actcaagaa ctgccagaat gtaactatct tctgatttct tggctcattg tgcacatgga
1201 ccatgtcatt gcaaggaac tggaaacaaa aatgaatata cagaacattt ctatagtct
1261 cagcccaact gtgcagatca gcaatcgagt cctgtatgtg ttttcacac atgtgcaaga
1321 actcttggga aatgtgttac taaagcaagt gatgaaacct ctgcgatggt ctaacatggc
1381 cacgatgccc acgtgccag agaccagggc gggcatcaag gaggagatca ggagacagga
1441 gtttctttt aattgtttac atcgagatct gcagggtggg ataaaggatt tgtctaaaga
1501 agaaagatta tgggaagtac aaagaattt gacagccctc aaaagaaaac tgagagaagc
1561 taaaagacag gagtgtgaaa ccaagattgc acaagagata gccagtcttt caaaagagga
1621 tgtttccaaa gaagagatga atgaaaatga agaagttata aatattctcc ttgctcagga
1681 gaatgagatc ctgactgaac aggaggagct cctggccatg gagcagtttc tgcgccggca
1741 gattgcctca gaaaaagaag agattgaacg cctcagagct gagattgctg aaattcagag
1801 tcgccagcag cacggccgaa gtgagactga ggagtactcc tccgagagcg agagcgagag
1861 tgaggatgag gaggagctgc agatcattct ggaagactta cagagacaga acgaagagct
1921 ggaaataaag aacaatcatt tgaatcaagc aattcatgag gagcgcgagg ccatcatcga
1981 gctgcgcgtg gcgtgcggc tgcctcagat gcagcgagcc aaggccgagc agcaggcgca
2041 ggaggacgag gagcctgagt ggcgcggggg tgccgtccag ccgccagag acggcgctct
2101 tgagccaaaa gcagctaaag agcagccaaa ggcaggcaag gagccggcaa agccatcgcc
2161 cagcagggat aggaaggaga cgtccatctg agcagcctgc gtggccgtct ggagtccgtg
2221 agactgaaa gacccgtgca tcttactgta acccgggggc caggccggct ctctcgctgt
2281 acattctgta aaggtgtctt ctctctcag actctctc tgcacacgt ctgactcctt
2341 cacgtcaggc tcaggttcca tgggaggacg aagcagtggg cgattgtgg gctttaggga
2401 cagatgagtt ttccagatag tgcagctta ttgaagatt aatttcttt gttaacttaa
2461 aataactatt ttaaccttg agtggcttct ttttaacca aaaaccgtct tctttgctt
2521 tttatcaca gcagaatcag gatctcttc tcatcaagg ggggaaccac accaggctag
2581 cgtcgcgcct gctgtggccg ccgcgagcca cgccctctgg gatctctggt accgtcactc
2641 ttgctgtgc ctccacacc ttctcgtg agatccctat gggggagctg cctcacgttc
2701 tctgactggt cagagcagcg cctggtggtt gttccctggc ccactctct ctctctctt
2761 gcagttctaa accacagtct ataagcccga gtcaccagga cggcctgtct ggccacagac
2821 aggggctgcc tgtggagcct gccacccggc ccccggcagt gcagtccagc ggggaggagg

```

**Figure 12. (Page 26 of 33)**

2881 ctgcccgttc ctgccagttc ctactgcgg ggaccagcaa aggcctctc actgggttg  
2941 tcaaaggtag tcacctggc ctggtgcatc cacagaggat gttgtcaaa ccagaaatct  
3001 tttaaagcac tgaccttct taaaaacaga atgactccga ttgcttgctt gggctagaat  
3061 gtacacgtct ccttgctga ataagccata tatatgctt taaacaaaag ttgaaatta  
3121 tccatatcat ctactgaac ctactggtg actccaatt gacaagattg agcaatagaa  
3181 aaaaattcct ttctttgaa tgaatgctg gattacccc accccattt ctgtttctg  
3241 gtccatccga tgagacgat gctctgatc tctgaggctt ctgggaggct gggccctgga  
3301 ggcaacgtgc tgcaggcgca ctctgcaga gtgaacagca ccgcgagaca ggccaggctc  
3361 gtggctcga agacaaacc cacacacact caaggggtcg aaaacaaacc ccacacgagg  
3421 gctctcacct ccttctcta gtagtattt atttcagca cctgttgat gcagtttta  
3481 atcctctacc tattgcactg ttgtgactg ttggccatta ttgattttg gtacgaaaaa  
3541 aagctttgt atagaaatca gcatactatt ttttaaatc tggagagaag atattctgt  
3601 gactgaaagt alggtcggg gtcatagata aatgtgcaa tgcctcttg ctgtcctgc  
3661 ggtctcagta cgttcactt atagctgct gcaatatga aggttcttt ttgtttgt  
3721 taaactcaa ttctatcaa ggtgcatgg attttaaaa ttagtattc attacaaatg  
3781 tctcagcatt ggtaactaa ttltggcag gaccattatt gatcaagcaa ataaattcaa  
3841 cagccatttg gaaaaaag

**Protein sequence of Human RLIP76**

MTECFLPPTSSPSEHRRVEHGSGLTRTPSSEEISPTKFPGLYRT  
GEPSPPHDILHEPPDVSDDEKDHGKKKGKFKKKEKRTEGYAAFQEDSSGDEAESPSK  
MKRSKGIVFKKPSFSKKKEKDFKIKEKPKEEKHKKEEKHKKEKSKDLTAADV  
KQWKEKKKKKKPIQEPEVPQIDVNLKPIFGIPLADAVERTMMYDGIRLPVAFRECID  
YVEKYGMKCEGIYRVSGIKSKVDELKAAYDREESTNLEDYEPNTVASLLKQYLRLPE  
NLLTKELMPRFEEACGRTTETEKVQEFQRLLKELPECNYLLISWLIVHMDHVIAKELE  
TKMNIQNISIVLSPTVQISNRVLYVFFTHVQELFGNVVLKQVMKPLRWSNMATMPTLP  
ETQAGIKEEIRRQEFLLNCLHRDLQGGIKDLSKEERLWEVQRILTALKRKLREKRQE  
CETKIAQEIASLSKEDVSKEEMNENEEVINILLAQENEILTEQEELLAMEQLRRQIA  
SEKEEIERLRAEIAEIQSRQQHGRSETEEYSSSESESESEDEEELQIILEDLQRQNEEL  
EIKNNHLNQAIHEERAIILRVQLRLLQMQRAKAEQQAQEDEEPEWRGGAVQPPRDG  
VLEPKAAKEQPKAGKEPAKPSRDRKETS

**Figure 12. (Page 27 of 33)**

**W26677. 11f7 Human retina...[gi:1305788]**

TNNNNNTTNNNNNNNTTNNCCTTGCTCAGCATTGGNTNTGATGTGCTGGTGGAGAACCACG  
AAGAATGNATTGCTGAGGGGAGACCTGGTCCAGGGTCTTCTCCCCTGTAATCCAGGGCCA  
CACTGATGAGNTCTGGGGGNTCTGCACACACCCCTCCCAGAACCGNTTCCTCACCTGCGG  
CCACGACCGGNAGTTCTGCCTGTGGGATGGGGAGAGCCATGCACTGGCCTGGAGCATCGA  
CCTCAAGGAGACTGGTCTCTGTGCTGACTTCCACCCGAGTGGGGCAGTTGTGGCCGNAGG  
ACTGAACACGGGGAGGTGGTTGGTTTTGGNCACAGAGACCAGAGAGATCGTGTCTGATGT  
CATTGATGGCAATNAGCAGCTCTCAGTGGTCCGGTACAGNCCAGATGGGTTGGTCCTGGC  
CCAATTGGTTCCCATNACAACNTNATNTTCAATCTTTNGNGGTTTCCAGGGGATGGTG  
CCCAATTCCAGNCCNTTTTGGGCCNTTTGTNTTTGGGTCAACNCCCAGNTTCAACCACTC  
AATNTTGGAGTAGGTTCAANNNTTNGNNTTACCAGTTGNNNTTNTCCAANNNNNNNNNNNN  
NNTNTNNNNNTNNTTNTTCTTTTNCNTNANNCNNNNNNNNNNNNCENNNTCTNCNTNTTNTC  
AANCCNNNTNNNNNNNCNNNCNNNNNCNTNTNCTNCTNNNNNCNNTNNNNCTNNTNNN  
CNNNNCTNNNNNTNNNCNNNNNNNN

**Protein sequence of Human retina cDNA**

No Protein sequence available from GenBank

**Figure 12. (Page 28 of 33)****X51804. Human PMI gene fo...[gi:35534]****Human PMI gene for a putative receptor protein**

```
1 ggcccccccc cccctagaa atgctgaac caggacggct cctggagtcc tcgcgcctc
61 gcagaaggac tacgggcccc ggcgaccccg ggggcggggc ttccggcgcg ctgccttg
121 ggcacggtag ttccgccggg tctggcttcc gcctgccgag cggccccgga ccgcaggccg
181 gactacactt cccgtcggcc cgcctgctct cccgatgccg ccttggcgcg agacgttggc
241 aagcagagtg tctccaagat ggccgcttgg ggaaggaggc gtcttgccc gggcagcagt
301 ggcggcagcg cccgagagag ggtgagcttg tcggccacag actgctacat tgtcatgag
361 atctacaatg gggagaatgc ccaagaccag ttgagtacg agctggagca ggccctggaa
421 gccagtaga agtacattgt gattagccc actcgattg gcgacgagac agcccgtgg
481 atcaccgtgg gcaactgcct gcacaagacg gccgtgctgg cgggcaccgc ctgcctctc
541 acccgttgg cgctgccctt agattattcc cactacattt cctgcccgc tgggtgctg
601 agctggcct gctgcacct ctatgggac tctggcagt ttgaccttg ctgaagtac
661 caagtggagt acgacgcta taaactgtcg cgcctgcctc tgcacacact cacctctcc
721 acccgggtgg tgctgggccg gaaggacgac ctgcacagaa agagactgca caacacgata
781 gcactggccg ccttgggtga ctgtgtaaag aagatttacg aactctatgc cgtatgatt
841 cagtagaaca gggagcgaag caaaaccacc cggcccacaa gagacaacag agtattcaga
901 tcgccacact ctgtaggga gcagagcctg ggcaggtgtt tggcttagta ttgttatt
961 ttaaaaaata acagatcacg ggtgtacca gggttttca gtcattaca ctaagatgtg
1021 gatttccata acccaagagg ggggtctgag gctgtggaag tccgactggg cagtggaaatg
1081 ctgatggagg cagacgctgc cgaggggggtg tggacgtgct ttgggggagg tctttaagtc
1141 tattgtttaa ctgtaccatc cagagccac cagaagctat tgatcattaa aattatgaga
1201 attcaactc c
```

**Protein sequence of Human PMI**

```
MAAWGRRRLGPGSSGGSARERVSLSATDCYIVHEIYNGENAQDQ
FEYELEQALEAQYKYIVIEPTRIGDETARWITVGNCLHKTAVLAGTACLFPLALPLD
YSHYISLPAGVLSLACCTLYGISWQFDPCKYQVEYDAYKLSRLPLHTLSSTPVVLV
RKDDLHRKRLHNTIALAALVYCVKKIYELYAV
```

**Figure 12. (Page 29 of 33)****M24069. Human DNA-binding...[gi:181483]****Human DNA-binding protein A (dbpA) gene, 3' end**

```

1 gaattcgggc gggggagccc aaggagcgag cgcgccagac gaagctcgag ccgcctccgc
61 cagcgcgacc ccacctcggc cgccggcctg cgccgcgaga tccgccccgg cctccccgag
121 agcgagcccc ggccgcccgcg accaccagcc gcgctaaccg ccgaccaacc gccaccgagg
181 cgctgagcg agagcagagg aggaggaggc atgagtgagg cgggcgaggc caccaccacc
241 accaccacca cctccccga ggctccgacg gaggcggccg ccgcggctcc ccaggacccc
301 gcgccaaga gcccgggtgg cagcgggtgc cccagggccg cgccccggc gcccgccgcc
361 cagctcgag gaaaccccg tgggacgcg gccctgcag ccacgggcac cgcggccgcc
421 gcctcttag ccgccggcg cggcagcgaa gacgcggaga aaaaagtct cgcaccaaaa
481 gtcctggca ctgtcaaatg gttaacgtc agaaatggat atggatttat aaatcgaaat
541 gacacaaaag aagatgtatt tgtacatcag actgccatca agaagaataa cccacggaaa
601 tatctgcgca gtgtaggaga tggagaaact gtagagttg atgtggttga aggagagaag
661 ggtgcagaag ctgccaatgt gactggcccg gatggagttc ctgtggaagg gagtctttac
721 gctgcagatc ggcgcggtta cagacgtggc tactatggaa ggcgcggtgg cctccccggg
781 aattacgtc gggaggagga ggaggaaggg agcggcagca gtgaaggatt tgacccccct
841 gccactgata ggcagttctc tggggcccg aatcagctgc gccgccccca gtatcgccct
901 cagtaccggc agcggcggtt cccgccttac cagtggtgac agaccttga ccgtcgctca
961 cgggtcttac ccatcccaa cagaatacag gctggtgaga ttgagagat gaaggatgga
1021 gtccagagg gagcacaact tcagggaccg gtcatcgaa atccaactta ccgccaagg
1081 tacctagca ggggacctc tcgccacga cctgccccag cagttggaga ggctgaagat
1141 aaagaaaatc agcaagccac cagtgttcca aaccagccgt ctgtcgccg tggataccg
1201 cgtccctaca attaccggc tcgcccgccg tctcctaac gtcctctac aagatggcaa
1261 agaggccaag gcaggatga cccaactga gaacctgct caccacccc agcagagcag
1321 tgtagtaac accaggctcc tcaggcacct tcacctcg caggtggacc taaagaatta
1381 gatgaccatt cagaaataaa gcaaaaagca ggccacatac ctaaccaac accaaagaaa
1441 catccaagca ataaagtga agactaacca agattggac attggaatgt ttactgttat
1501 tcttaagaa acaactacaa aaagaaaatg tcaacaaatt ttccagcaa gctgagaacc
1561 tggaattc

```

**Protein Sequence of Human DNA-binding protein A (dbpA)**

```

EFGRGSPRSEARRSSSLRQRDPTSAAGLRREIRPGLPESEPR
PPRPPAALTADQPPPRRLSESRGGGMSEAGEATTTTTTLPQAPTEAAAAAPQDPAP
KSPVSGSAPQAAAPAPAAHVAGNPGDAAPAATGTAAAASLAAAAGSEDAEKKVLATK
VLGTVKWFNVRNGYGFINRNDTKEDVFVHQTAIKKNNPRKYLRVSGDGETVEFDVVEG
EKGAEEANVTGPDGVPVEGSRYAADRRRYRRGYGRRRGPPRNYAGEEEEEEGSGSSEG
FDPPATDRQFSGARNQLRRPQYRQYRQRRFPYHVGQTFDRRSRVLPHPNRIQAGEI
GEMKDGVPGEAQLQGPVHRNPTYRPRYRSRGPPRPRPAPAVGEAEDKENQQATSGPNQ
PSVRRGYRRPYNYRRPPSS

```

**Figure 12. (Page 30 of 33)**

NM\_002218. Homo sapiens inte...[gi:4504784]:

Homo sapiens inter-alpha (globulin) inhibitor H4 (plasma Kallikrein-sensitive glycoprotein) (ITI4)

DNA sequence:

```
1 gtgagaagcc tcttggcaga cactggagcc acgatgaagc cccaaggcc tgtccgtacc
61 tgcagcaaag ttctgtctct gctttactg ctggccatcc accagaccac tactgccgaa
121 aagaatggca tcgacatcta cagcctcacc gtggactcca gggctcacc ccgatttgcc
181 cacacggtcg tcaccagccg agtggtaaat agggccaata cggtagagga ggccaccttc
241 cagatggagc tgcccaagaa agccttcacc accaactct ccatgaacat cgatggcatg
301 acctaccagc ggatcatcaa ggagaaggct gaagcccagg cacagtacag cgagcagtg
361 gccaaaggaa agaagcgtgg cctgtcaag gccaccggga gaaacatgga gcagtccag
421 gtgtcggcca gtgtggctcc caatgccaag atcaccttg agctggctca tgaggagctg
481 ctaagcggc gtttgggggt gtacgagctg ctgctgaaag tgcggcccca gcagctggc
541 aagcacctgc agatggacat tcacatcttc gagccccagg gcatcagctt tctggagaca
601 gagagcacct tcagaccaa ccagctggta gacgacctca ccactggca gaataagacc
661 aaggctcaca tccgggtcaa gccaacactt tccagcagc aaaagtcccc agagcagcaa
721 gaaacagtc tgagcggcaa cctcattatc cgctatgatc tggaccgggc catctccggg
781 ggctccattc agatcgagaa cggctacttt gtacactact ttgccccga gggcctaacc
841 acaatgcca agaattgtgt cttgtcatt gacaagagcg gctccatgag tggcaggaaa
901 atccagcaga cccgggaagc ctaatacaag atcctggatg acctagccc cagagaccag
961 ttcaacctca tcgtcttcag tacagaagca actcagtga ggccatcact ggtgccagcc
1021 tcagccgaga acgtgaacaa ggccaggagc ttgtctcgg gcatccaggc cctgggaggg
1081 accaatalca atgatgcaat gctgatggct gtgcagttgc tggacagcag caaccaggag
1141 gagcggctgc ccgaaggag gtgtcactc atcatctgc tcaccgatg cgacccact
1201 gtgggggaga ctaacccag gagcatccag aataacgtgc ggaagctgt aagtggccgg
1261 tacagcctct tctgctggg ctctggttc gacgtcagct atgcttctt ggagaagctg
1321 gactggaca atggcgccct ggccggcgc atccatgagg actcagactc tgcctgcag
1381 ctccaggact taccagga agtggccaac ccactgtga cagcagtgac ctccagtag
1441 ccaagcaatg ccgtggagga ggtcactcag acaacttcc ggctcctct caagggtca
1501 gagatgtggt tggctgggaa gctccaggac cgggggctg atgtgtcac agccacagc
1561 agtgggaagc tgctacaca gaacatcact ttccaaacgg agtccagtg ggcagagcag
1621 gagcgaggat tccagagccc caagtatac ttccaaact tcattggag gctctgggca
1681 tactgacta tccagcagct gctggagcaa actgtctcc catccgacgc tgatcagcag
1741 gccctccgga accaagcgt gaatttatca ctgcttaca gcttctcac gccttcaca
1801 tctatggtag tcacaaacc cgaatgacaa gagcagctc aagttgtga gaagccatg
1861 gaaggcgaaa gtagaaacag gaatgtccac tcaggtcca ctttctcaa atattatc
1921 caggagcaa aaataccaaa accagaggct tcttttctc caagaagagg atggaataga
1981 caagctggag ctgctggctc ccgatgaat ttcagacctg ggttctcag ctccaggcaa
2041 ctggactcc caggacctcc tgatgtctt gacctgctg ctaccaccc ctccgccgt
2101 ctggcatct tgcctgttc agcaccacca gccacctcaa atcctgatcc agctgtgtt
2161 cgtgtcatga atatgaaaat cgaagaaaca accatgacaa cccaaacccc agccccata
2221 caggctccct ctgcatctt gccactgcct gggcagagtg tggagcggct ctgtgtggc
2281 ccagacacc gccaggggac agtgaacctg ctctcagacc ctgagcaagg ggttgaggc
2341 actggccagt atgagagggg gaaggctggg ttctcatgga tcgaagtgc ctcaagaac
2401 cccctggtat ggtttcacgc atccctgaa cagtggtgg tgactcggaa ccgaagaagc
2461 tctgcgtaca agtgaagga gacgtatc tcagtatgc ccggcctgaa gatgacctg
2521 gacaagacgg gtctctgt gctcagtgac ccagacaaag tgacctcgg cctgtgttc
2581 tggatggcc gtggggagg gctccggctc ctctgcgtg aactgaccg ctctccagc
2641 caggttgag ggaccttg ccagtttac caggaggtgc tctggggtc tccagcagc
2701 tcagatgac gcagacgcac gctgagggtt cagggcaatg accactctgc caccagagag
```



**Figure 12. (Page 31 of 33)**

2761 cgcaggctgg attaccagga ggggcccccg ggagtgagga ttctctgctg gtctgtggag  
2821 ctgtagtct gatggaagga gctgtgcca ccctgtacac ttggcttccc cctgcaactg  
2881 cagggccgct tctggggcct ggaccacat ggggaggaag agtcccactc attacaaata  
2941 aagaaagggtg gtgtgagcct ggg

Protein sequence for Homo sapiens inter-alpha (globulin) inhibitor H4 (plasma Kallikrein-sensitive glycoprotein) (ITI4):

MKPPRPVRTCSKVLVLLSLLAIHQTTTAEKNGIDIYSLTVDSRVSSRFAHTVVTSRVVRANTVQEATFQMELPKKAFIT  
NFSMNIDGMTYPGIIKEKAEQAQYSAAVAKGKNAGLVKATGRNMEQFQVSVSVAPNAKITFELVYEELLKRRLGVYE  
LLLKVRPQQLVKHLQMDIHIFEPQGISFLETSTFMTNQLVDALTTWQNKTKAHIRFKPTLSQQQKSPEQQETVLDGNL  
IIRYDVEDRAISGGSIQIENGIFYVHYFAPEGLTTPKNNVFVIDKSGSMSGRKIQQTREALIKILDDLSPRDQFNLIWFSTE  
ATQWRPSLVPASAENVNKARSFAAGIQALGGTNINDAMLMVQLLDSSNQEERLPEGSVSLIILLTDGDPTVGETNPR  
SIQNNVREAVSGRYSLFCLGFGFDVSYAFLEKLALDNGGLARRIHEDSDSALQLQDFYQEVANPLLTAVTFEYPSNAV  
EEVTQNNFRLLFKGSEMVVAGKLQDRGPDVLTATVSGKLPTQNITFQTESSVAEQEAEFQSPKYIFHNFMERLWAYL  
TIQQLLEQTVSASDADQQALRNQALNLSLAYSFVTPLTSMVVTKPDDQEQSQVAEKPMEGESRNRNVHSGSTFFKYY  
LQGAIPKPEASFSPRRGWNRRQAGAAGSRMNRPGVLSSRQLGLPGPPDVPDHAAYHPFRRLLPASAPPATSNP  
DPAVSRVMNMKIEETMTTQTPAPIQAPSAILPLPGQSVERLCVDPRHRQGPVNLLSDPEQGVETGQYEREKAGFS  
WIEVTFKNPLVWVHASPEHVVTNRNRSSAYKWETLFSVMPGLKMTMDKTGLLLSDPDKVTIGLLFWDGRGEGLR  
LLLRDTDRFSSHVGGTLGQFYQEVWLGSPAASDDGRRTLVRVQGNHDSATRERRLDYQEGPPGVEISCWSVEL

**Figure 12. (Page 32 of 33)**

NM\_000584. Homo sapiens interleukin 8 (IL8), mRNA.[gi:28610153]

```
1 ctccataagg cacaaacttt cagagacagc agagcacaca agcttctagg acaagagcca
61 ggaagaaacc accggaagga accatctcac tgtgtgtaaa catgactcc aagctggccg
121 tggctctctt ggcagccttc ctgattctg cagctctgtg tgaagggtga gtttgccaa
181 ggagtgtctaa agaacttaga tgtcagtga taaagacata ctccaaacct ttccaccca
241 aatttatcaa agaactgaga gtgattgaga gtggaccaca ctgcgccaac acagaaatta
301 ttgtaaagct ttctgatgga agagagctct gtctggaccc caaggaaaac tgggtgcaga
361 ggggtgtgga gaagttttg aagagggctg agaattcata aaaaaattca ttctctgtg
421 tatccaagaa tcagtgaaga tgccagtga acttcaagca aatctacttc aacacttcat
481 gtattgtgtg ggtctgtgt aggggtgcca gatgcaatac aagattctct gttaaattg
541 aatttcagta aacaatgaat agttttcat tgtacatga aatatccaga acatacttat
601 atgtaaagta ttatttatt gaatctacaa aaaacaacaa ataatttta aatataagga
661 tttcctaga tattgcacgg gagaatatac aaatagcaaa attgaggcca agggccaaga
721 gaatalccga acttaattt caggaattga atgggttgc tagaatgtga tatttgaagc
781 atcacataaa aatgatggga caataaattt tgccataaag tcaaattag ctggaatcc
841 tggattttt tctgttaa atctgcaacc tagtctgcta gccaggatcc acaagtcctt
901 gttccactgt gccttggtt ctctttatt tctaagtga aaaagtatta gccaccatct
961 taccctcacg tgatgtgtg aggacatgtg gaagcactt aagtttttc atcataacat
1021 aaattattt caagtgaac ttattaacct atttattt tatgtatta ttaagcatc
1081 aaatattgt gcaagaattt gaaaaaatag aagatgaatc attgattgaa tagttataa
1141 gatgttatag taaatttatt ttattttaga tattaaatga tgtttatta gataaattc
1201 aatcagggtt ttagattaa acaacaaac aattgggtac ccagttaaat ttcatattca
1261 gataaacaac aaataattt ttagtataag tacattattg ttatctgaa attttaattg
1321 aactaacaat ctagtttga tactcccagt ctgtcattg ccagctgtgt tggtagtgct
1381 gtgttgaatt acggaataat gagttagaac tattaaaaca gccaaaactc cacagtcaat
1441 attagtaatt tctgtctgt tgaactgtt ttattatga caaatagatt ctataatat
1501 tatttaaatg actgcattt taaatacaag gctttatatt ttaacttta agatgtttt
1561 atgtgctctc caaattttt ttactgttc tgattgtatg gaaatataaa agtaaatatg
1621 aaacatttaa aatataattt gttgtcaaag taaaaaaaaa aaaaaa
```

Protein sequence for Interleukin 8 precursor

```
1 mtsklavall aafliisaalc egavlprsak elrcqckty skpfhpkfik elrviesgph
61 canteiivkl sdgreldcp kenwvqvve kflkraens
```

**Figure 12. (Page 33 of 33)**

M11725. Human C-reactive protein gene, complete cds.[gi:181067]

```

1  ttgcttccc ctctcccca agctctgaca cctgcccaca caagcaatgt tggaaaatta
61  ttacatagt ggcgcaaact cccttactgc ttggatata aatccaggca ggaggaggta
121  gctctaaggc aagagatctg ggacttctag cccctgaact ttcagccgaa tacatctttt
181  ccaaaggagt gaaticaggc cctgtatca ctggcagcag gacgtgacca tggagaagct
241  gttgtgttc ttggtctga ccagcctctc tcatgcttt ggccagacag gtaagggcca
301  ccccaggcta tgggagagt ttgatctgag gtatgggggt ggggtctaag actgcatgaa
361  cagtctcaaa aaaaaaaaaa aaagactgta tgaacagaac agtggagcat cctcatggt
421  gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt tgtgtaactg gagaaggggt cagtctgtt
481  ctcaatctta aattctatac gtaagtgagg gatatagatct gtgtgatctg agaaacctct
541  cacatttctt tgttttctg gctcacagac atgtcgagga aggcctttgt gttcccaaa
601  gagtcggata ctctctatgt atccctcaaa gcaccgttaa cgaagcctct caaagccttc
661  actgtgtgcc tccacttcta caggaactg tcccgaccc gtgggtacag tattttctg
721  tatgccacca agagacaaga caatgagatt ctcatatttt ggtctaagga tataggatac
781  agttttacag tgggtgggtc tgaatatla ttcgagggtc ctgaagtcac agtagctcca
841  gtacacattt gtacaagctg ggagtcggcc tcagggatcg tggagttctg ggtagatggg
901  aagcccaggg tgaggaagag tctgaagaag ggatacactg tgggggcaga agcaagcatc
961  atcttggggc agggacagga ttccctcgtt gggaactttg aaggaagcca gtccctgggt
1021 ggagacattg gaaatgtgaa catgtgggac ttgtgctgt caccagatga gattaacacc
1081 atctatcttg gcgggccctt cagtctaat gtctgaact ggcgggcact gaagtatgaa
1141 gtgcaaggcg aagtgttac caaacccag ctgtggccct gaggccagct gtgggtcctg
1201 aaggtaacct ccggtttttt acaccgcatg ggccccacgt ctctgtctct ggtacctccc
1261 gctttttac actgcatggt tcccacgtct ctgtctctgg gccttgttc ccctatatgc
1321 attgaggcct gctccacct cctcagcgcc tgagaatgga ggtaaagtgt ctggtctggg
1381 agctcgtaa ctatgtctgg aaatgttcca aaagaatcag aatttgaggt gttttgttt
1441 cattttatt tcaagttgga cagatcttgg agataatttc ttacctaca tagatgagaa
1501 aactaacacc cagaaaggag aaatgatgtt ataaaaaact cataaggcaa gagctgagaa
1561 ggaagcgctg atcttctatt taattcccca cccatgaccc ccagaaagca ggagcattgc
1621 ccacattcac agggctcttc agtctcagaa tcaggacact ggccagggtgt ctggtttggg
1681 tccagagtgc tcatcatcat gtcatagaac tgcctggccc aggtctcctg aaatgggaag
1741 cccagcaata ccacgcagtc cctccacttt ctcaaagcac actggaaagg ccattagaat
1801 tggcccagca gagcagatct gcttttttc cagagcaaaa tgaagcacta ggtataaata
1861 tgtgttact gccaagaact taaatgactg gttttgttt gctgcagtg ctttctaatt
1921 ttatggctc ttctgggaaa ctctcccct ttccacacg aacctgttg ggctgtgaat
1981 tcttttca tccccgcat ccaatatac ccaggccaca agagtggacg tgaaccacag
2041 ggtgtcctgt cagaggagcc catctccat ctccccagct ccctatctgg aggatagttg
2101 gatagttacg tgttctagc aggaaccaact acagtcttc caaggattga gttatggact
2161 ttgggagtga gacatcttct tctgtctgga ttccaagct gagaggacgt gaacctggga
2221 ccaccagtag ccatcttgtt tgccacatgg agagagactg taggacaga agccaaactg
2281 gaagtggagg agccaaggga ttgacaaaca acagagcctt gaccacgtgg agtctctgaa
2341 tcagccttgt ctggaaccag atctacacct ggactgccca ggtctataag ccaataaagc
2401 cctgtttac ttgagtgagt ccaagctgtt ttctgatagt tgcttagaa gttgtgacta
2461 acttctctat gaccttgaa

```

Protein sequence for C-reactive protein

```

1  meklclflvl tsishafgqt dmsrkafvfp kesdtsyvsl kapltkplka ftvclhfyte
61  lsstrgysif syatkrqdn ilifwskdig ysftvggsei lfevpevtva pvhictswes
121  asgivefwvd gkprvrsklk kgytvgaeas iilgqeqlsf ggnfegsqsl vgdignvrnmw
181  dfvlspdein tiylgppfsp nvlwnralky evqgevftkp qlwp

```

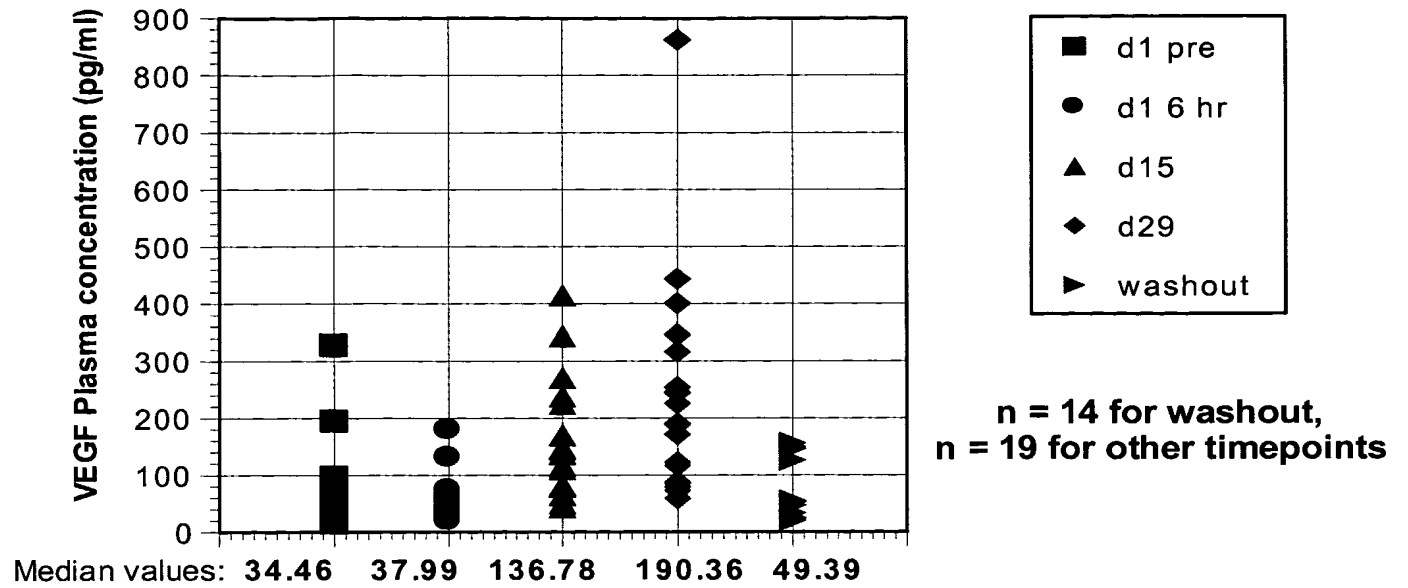
**Figure 13.**

Figure 14.

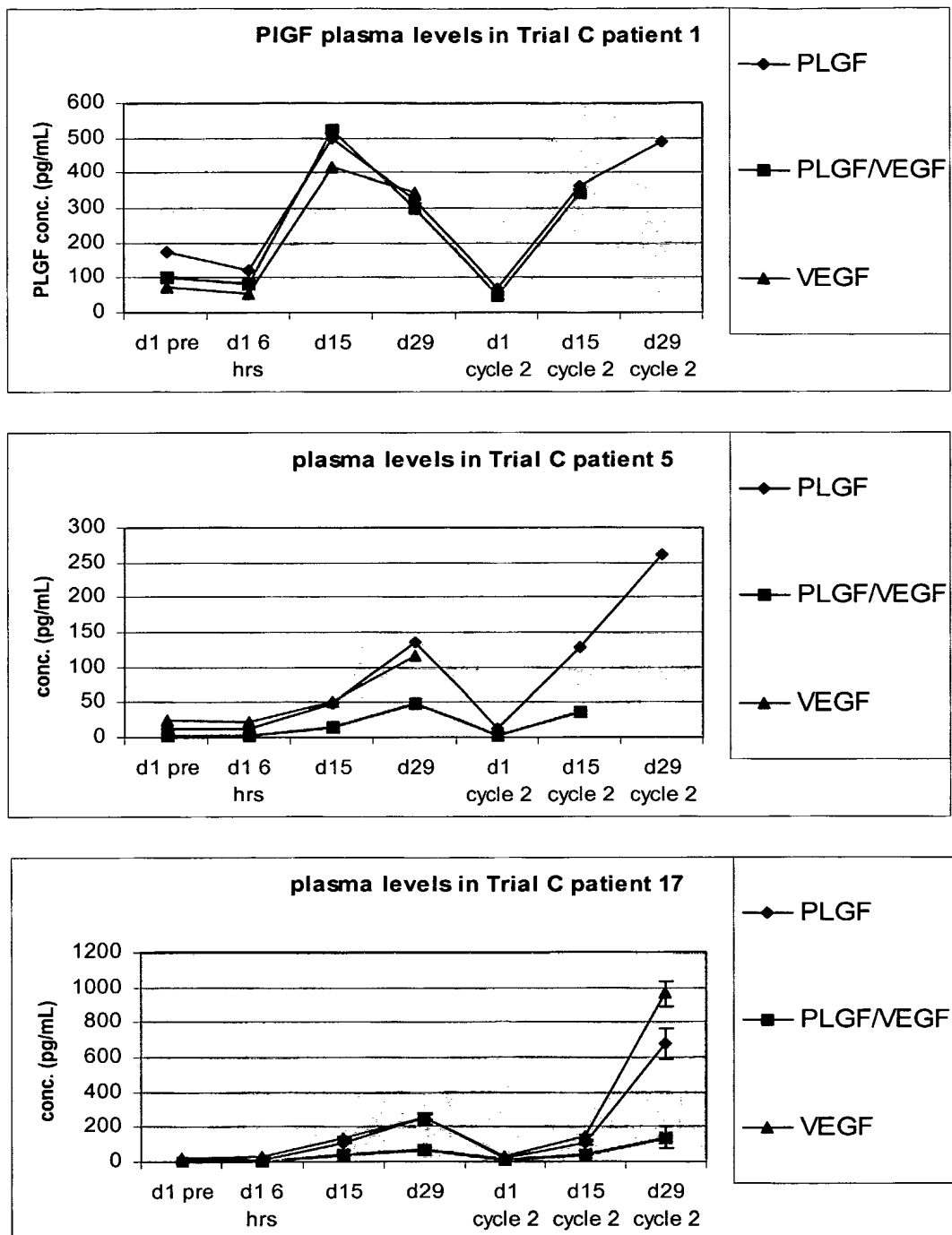
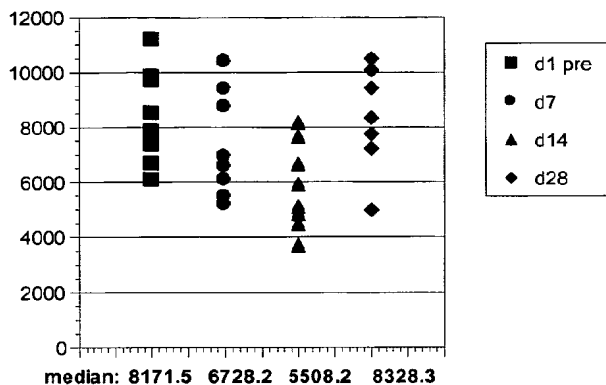
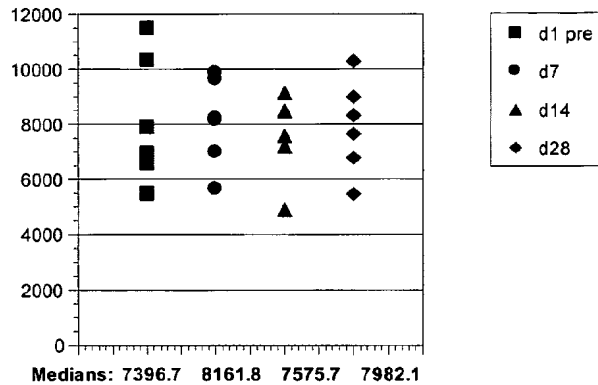


Figure 15.

sVEGFR2 plasma levels in 50 mg cohort (pts 1-6, 13-14)



sVEGFR2 levels in 25 mg cohort (pts. 7-12)



Graphs above display plasma levels of sVEGFR2 in individual patients, either 50 mg daily (A) or 25 mg daily (B). The table at right displays results of t-test analysis comparing sVEGFR2 plasma concentrations at end of dosing (d14) to day 1 or at end of cycle 1 washout (d28) to day 1.

|              | <u>d14 v d1</u> | <u>d28 v d1</u> |
|--------------|-----------------|-----------------|
| 50 mg cohort | 0.0076          | 0.94            |
| 25 mg cohort | 0.611           | 0.87            |

**t-test comparisons of sVEGFR2 levels in two cohorts**

Figure 16.

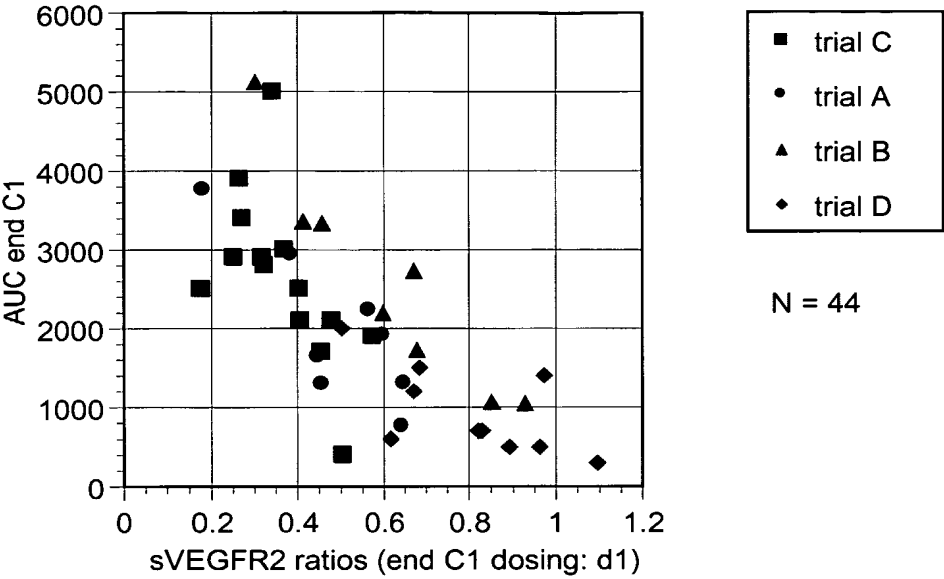
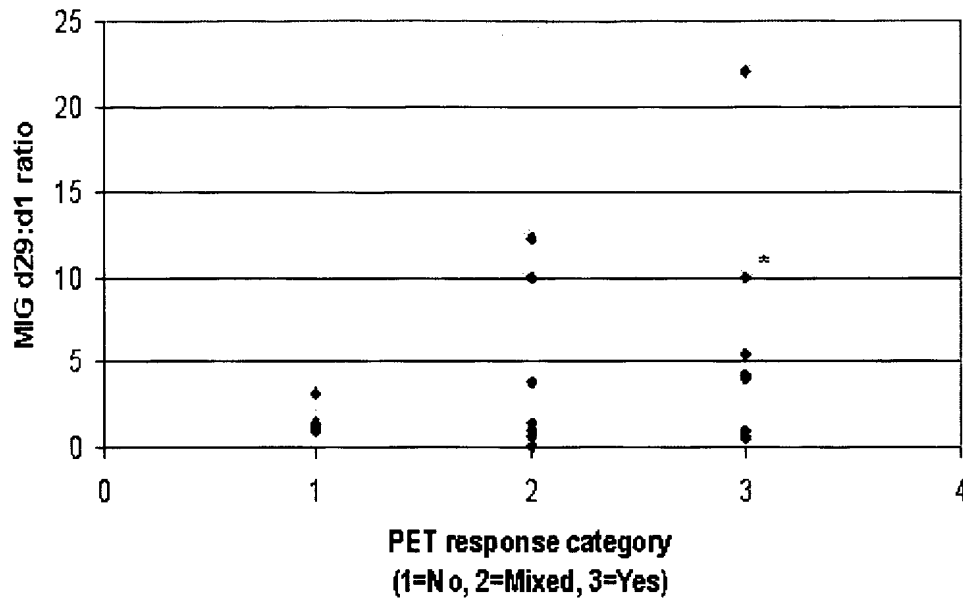


Figure 17.



1: n = 6. 2: n = 8. 3: n = 8

\*estimated minimum ratio



**Figure 18.****NP\_003367      vascular endothelial growth factor [gi:19923240]**

1 mnflswvhw slallylhh akwsqaapma eggqnhhev vkfmdvyqrs ychpietlvd  
61 ifqeypdeie yifkpscpl mrcggcsnde glecvptees nitmqimrik phqgqhigem  
121 sflqhnkcec rpkkdirarqe npcgpserr khlfvqdpqt ckcscknths rckarqlen  
181 ertcrecdkpr r

**Figure 19.****P49763      Placenta growth factor [gi:17380553]**

1 mpvmrlfpcf lqllaglalp avppqqwals agngssevev vpfqevwgrs ycralerlvd  
61 vvseyipseve hmfspscvsl lrtgccgde nlhcvpveta nvtmqllkir sgdrpsyvel  
121 tfsqhvrcec rhspgrqspd mpgdfradap sflpprrslp mlfrmewgca ltgsqsavwp  
181 sspvpeeipr mhpgrngkkq qrkplrekmk percgdavpr r

**Figure 20.****P35968      Vascular endothelial growth factor receptor 2 [gi:9087218]**

1 mqsksvllava lwlcvetraa svglpsvsld lprlsiqkdi ltikanttlq itcrgqrdld  
61 wlwpnnqsgs eqrvevtecs dglfckltli pkvigndtga ykcfyretld asviyvyvqd  
121 yrspfiassvs dqhgvyvite nknktvvipec lgsislnvs lcarypekrf vpdgnriswd  
181 skkgftipsy misyagmvfc eakindesyq simyivvvvg yriydvvlsp shgielsvge  
241 klvlnctart elnvgidfnw eypsskhqhk klvnrldktq sgsemkkfls tltidgvtrs  
301 dqglytcaas sglmtkknst fvrvehkpfv afgsgmeslv eatvgervri pakylgyppp  
361 eikwykngip lesnhtikag hvltimevse rdtgnytviil tnpiskekqs hvvslvyvvp  
421 pqigekslis pvdsyqygtt qtlctvyai ppphhihwyw qleeeacanep sqavsvtnpy  
481 pceewrsved fqggnkievn knqfaliegk nktvstlvic aanvsalykc eavnkvggrge  
541 rvisfhvtrg peitlqpdmq pteqesvslw ctadrstfen ltwyklgpqp lpihvgelpt  
601 pvcknldtlw klnatmfsns tndilimelk naslqdgdy vclaqrktk krhcvvrqlt  
661 vlervaptit gnlenqttsi gesievscta sgnpppqimw fkdnetlved sgivlkdgnr  
721 nltirrvrke deglytcqac svlgcakvea ffiiegaqek tnleiiilvg taviamffwl  
781 llviilrtvk ranggelktg ylsivmdpde lpldehcerl pydaskwefp rdrklgkpl  
841 grgafgqvie adafgidkta tctrvavkml kegathsehr almselkili highhlnvvn  
901 llgactkpgg plmvivefck fglnstylrs krnefvpykt kgarfrqgkd yvgaipvdlk  
961 rrldsittsq ssassgfvee ksldveeee apedlykdfl tlehlicysf qvakgmefla  
1021 srkcihrdla arnillsekn vvkicdfgla rdiykdpdyv rkgdarlpk wmapetifdr  
1081 vytiqsdvws fgvlleifs lgaspypgvk ideefcrrlk egtrmrapdy ttpemyqtml  
1141 dcwhgepsqr ptfselvehl gnllqanaqq dgkdyivlpi setlsmeeds glslptspvs  
1201 cmeeeevcdp kfhydntagi sqylqnskrk srpvsvktfe dipleepevk vipddnqtds  
1261 gmvaseelk tledrtklsp sfggmvpssks resvasegsn qtsqyqsyh sddtdttvys  
1321 seeaellkli eigvqtgsta qilqpdsgtt lssppv

**Figure 21.**

**Q07325      Small inducible cytokine B9 precursor (CXCL9) (Gamma interferon induced monokine) (MIG) [gi:585487]**

1 mkksgvlfl giillvligv qgtpvvrkgr cscistnqgt ihlqslkdlk qfapspseck  
61 ieiiatlknq vqtclnpdsa dvkelikkwe kqvsqkkkqk ngkqhkkkv lkvrksqrsr  
121 qkkt

**Figure 22.**

**NP\_001556**            **interferon-inducible cytokine IP-10 [gi:4504701]**

1 mnqtailicc lifltlsgiq gvplsrtrvc tcisisnqpvr nprlekley ipasqfcprv  
61 eiatmkkkg ekrcnpsk aiknllkavs kemskrsp

**Figure 23.**

**O14625      Interferon-inducible T-cell alpha chemoattractant (I-TAC)[gi:7674360]**

1 msvkgmaial avilcatvvq gfpmfkggrc lcigpgvkav kvadiekasi mypsnncdki  
61 eviitlkenk gqrclnpksk qarliikkve rknf

**Figure 24. (Page 1 of 46)****M33308. Human vinculin mR...[gi:340236]****Human vinculin mRNA, complete cds**

```

1 gaattccact tctctgtcgc ccgcgggtcg ccgccccgct cgcgcgcgcg atgccagtgt
61 ttcatacgcg cagcatcgag agcatcctgg agccgggtggc acagcagatc tccacctgg
121 tgataatgca cgaggaggcg gaggtggacg gcaaagccat tctgacctc accgcgcccc
181 tggccgccgt gcaggcggcc gtcagcaacc tcgtccgggt tggaaaagag actgttcaaa
241 ccactgagga tcagatttg aagagagata tggcaccagc atttattaag gttgagaatg
301 cttgcaccaa gctgtccag gcagctcaga tgcctcagtc agacccttac tcagtgcctg
361 ctcgagatta tctaattgat gggtaagggt gcacctctc tggaacatca gacctgtcc
421 ttaccttca tgaggctgag gtccgtaaaa ttattagagt ttgcaaagga attttggat
481 atcttacagt ggcagagggt gtggagacta tggaagattt ggctacttac acaaagaatc
541 ttgggccagg aatgactaag atggccaaga tgattgacga gagacagcag gagctcactc
601 accaggagca ccgagtgatg ttgtgaact cgtgaacac cgtgaaagag ttgctgccag
661 ttctcattc agctatgaag attttgtaa caactaaaaa ctcaaaaaac caaggcatag
721 aggaagcttt aaaaaatcgc aattttactg tagaaaaaat gagtgtgtaa attaagtaga
781 taattcgtgt gttacaactc acctcttggg atgaagatgc ctgggccagc aaggacactg
841 aagccatgaa gagagcattg gcctccatag actccaaact gaaccaggcc aaagggtggc
901 tccgtgacct tagtgcctcc ccaggggatg ctggtgagca ggccatcaga cagatcttag
961 atgaagctgg aaaagttggt gaactctgtg caggcaaaga acgcaggagc attctgggaa
1021 cttgcaaaat gctagggcag atgactgac aagtggctga cctccgtgcc agaggacaag
1081 gatcctcacc ggtggccatg cagaaagctc agcaggtatc tcagggtctg gatgtgctca
1141 cagcaaaagt ggaaaatgca gtcgcaagc tggaagccat gaccaactca aagcagagca
1201 ttgcaaagaa gatcgatgct gtcagaact ggctgcaga tccaaatggt ggaccggaag
1261 gagaagagca gattcgaggt gctttggctg aagctcggaa aatagcagaa ttatgtgatg
1321 atcctaaaga aagagatgac attctacgtt cctttgggga aatatctgct ctgactcta
1381 aattagcaga tctacgaaga caggggaaag gagattctcc agaggctcga gccttggcca
1441 aacagggtgc cacggccctg cagaacctgc agacaaaac caaccgggct gtggccaaca
1501 gcagaccggc caaagcagct gtacaccttg agggcaagat tgagcaagca cagcggtgga
1561 ttgataatcc cacagtggat gaccgtggag tcggtcaggc tgccatccgg gggcttgttg
1621 ccgaagggca tcgtctggct aatgttatga tggggcctta tcggcaagat ctctcgcca
1681 agtgtgaccg agtggaccag ctgacagccc agctggctga cctggctgcc agagggggaa
1741 gggagagtcc tcaggcacga gcacttgcac ctgagctcca agactcctta aaggatctaa
1801 aagctcggat gcaggaggcc atgactcagg aagtgtcaga tgtttcagc gataccacaa
1861 ctcccatcaa gctgttggca gtggcagcca cggcgccctc tgatgcgcct aacagggaag
1921 aggtatttga tgagagggca gctaactttg aaaaccattc aggaaagctt ggtgctacgg
1981 ccgagaaggc ggctgcggtt ggtactgcta ataatcaac agtggaaggc attcaggcct
2041 cagtgaagac ggcccagaaa ctacaccccc aggtggtctc ggctgctcgt atcttactta
2101 ggaaccttgg aaatcaagct gcttatgaac attttgagac catgaagaac cagtggatcg
2161 ataattgtga aaaaatgaca gggctggttg acgaagccat tgatacaaaa tctctgttgg
2221 atgcttcaga agaagcaatt aaaaaagacc tggacaagtg caaggtagct atggccaaca
2281 ttacgcctca gatgtgtgtt gctggggcaa ccagtattgc tcgtcgggcc aaccggatcc
2341 tgctggtggc taagaggag gtggagaatt ccgaggatcc caagtccgt gaggtgtga
2401 aagctgcctc tgatgaattg agcaaaacca tctcccaat ggtgatggat gcaaaagctg
2461 ttgctggaag catttccgac cctggactgc aaaagagctt cctggactca ggatatcgga
2521 tcttgggagc tgtggccaag gtcagagaag cttccaacc tcaggagcct gactccccgc
2581 gcctccacc agacctgaa caactccgac taacagatga gcttgcctct cccaaaccac
2641 ctctgcctga aggtgaggtc cctccaccta ggctccacc accagaggaa aaggatgaag

```

**Figure 24. (Page 2 of 46)**

2701 agttccctga gcagaaggcc ggggaggtga ttaaccagcc aatgatgatg gctgccagac  
2761 agctccatga tgaagctcgc aaatggtcca gcaagggcaa tgacatcatt gcagcagcca  
2821 agcgcatggc tctgctgatg gctgagatgt ctcggctggt aagagggggc agtggtacca  
2881 agcgggcact cttcagtggt gccaaggaca tcgccaaggc ctcagatgag gtgactcggg  
2941 tggccaagga ggttgccaag cagtgcacag ataaacggat tagaaccaac ctcttacagg  
3001 tatgtgagcg aatcccaacc ataagcacc agtcaaaaat cctgtccaca gtgaaggcca  
3061 ccatgctggg ccggaccaac atcagtgatg aggagtctga gcaggccaca gagatgctgg  
3121 ttacaatgc ccagaacctc atcagtgatg tgaaggagac tgtgcgggaa gctgaagctg  
3181 ctcaatcaa aattcgaaca gatgctggat ttactctgcg ctgggttaga aagactccct  
3241 ggtaccagta ggcacctggc tggcctggc tggcacagaa acctctacta aaaagaagga  
3301 aaatgatctg agtcccagga gctgccaga gttgctggga gctgaaaaat cacatcctgg  
3361 cctggcacat cagaagggaa tgggggcctc ttcaaattag aagacattta tactctttt  
3421 tcatggacac ttgaaatgt tttctgtat aaagcctgta ttctcaaaca cagttacact  
3481 tgtgcaccct ctatcccaat aggcagactg ggtttctagc ccatggactt cacataagct  
3541 cagaatccaa gtgaacacta gccagacact ctgctctgcc cttgttccct aggggacact  
3601 tccctctgtt tctcttccct tggtcccat tcactctcc agaatcccaa gaccagggc  
3661 ccaggcaaat cagtactaa gaagaaaatt gctgtgcctc ccaaattgt tttgagctt  
3721 ccatgttctg gccaacata cttctctcc ctgggctgtg ctacctgggt cttttcaga  
3781 agtgagcttt gctgtacag gggaagggtg cctctgtgga gcccagcat atgggggcct  
3841 ggattcattt cctgccctc ctcagtttaa tcttctagt tcccacaat ataaaactgt  
3901 acttcaatgt caggaagaaa tcacagaatc atatgattct gctttacca tgcccctgag  
3961 caatgtctgt gctagggaaa ctcccgtcc catatctgc ctcagcccgc caaggtagcc  
4021 atccatgaa cacactgtgt cctggtgctc tctgccactg gaagggcaga gtagccaggg  
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4201 tgaaatctg cattttaatt ttaacaaaa catgtctcct atatcctggt tttgtagcc  
4261 ttctccaca tctttctaa acaagatttt aaagacatgt aggtgtttgt tcatctgtaa  
4321 ctctaaaaga tcttttttaa attcagtcct aagaaagg agtgcttgc ccctaagagt  
4381 gtttaattgc aaggcagccc tgtctgaagg acacttctg cctaaggag agtggtattt  
4441 gcagactaga attctagtgc tgtgaagat gaatcaatgg gaaatactac tctgtaatt  
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4561 caagagagta atgggtttca ttttctat caccacagta agttctact aggcaaaatg  
4621 agagggcagt gtttctttt tggtaactat tactgctaag tattcccag cacatgaaac  
4681 cttattttt ccaaagccag aaccagatga gtaaaggagt aagaacctg cctgaacatc  
4741 ctctctccc acccatcgtc gtgtgttagt tccaacatc gaatgtgtac aacttaagt  
4801 ggtcctttac actcaggctt tcaatttc ctttaaatg aggatgatta tttcaaggc  
4861 cctcagcata ttgtatagt tgttgctg atataaatgc aatattaatg ctttaaggt  
4921 atgaatctat gccaaagatc actgtgtgt ttactaaaga aagattact agaggaaata  
4981 agaaaaatca tgttgcctc cccgttctt ccagtgttt gagacactgg ttacacttt  
5041 atgccggatg tgttttctc caatatcagt gctcgagaca cagtgaagca aattaaaaa  
5101 aa



**Figure 24. (Page 3 of 46)****Protein Sequence of Human vinculin:**

MPVFHTRTIESILEPVAQQISHLVIMHEEGEVDGKAIPDLTAPV  
AAVQAAVSNLVRVGKETVQTTEDQILKRDMPPAFIKVENACTKLVQAAQMLQSDPYSV  
PARDYLDGSRGILSGTSDLLLTfDEAEVRKIIRVCKGILEYLTVAEVVETMEDLVTY  
TKNLGPGMTKMAKMIDERQQELTHQEHVMLVNSMNTVKELLPVLISAMKIFVTTKNS  
KNQGIEEALKNRNFTVEKMSAEINEIIRVLQLTSWDEDAWASKDTEAMKRALASIDSK  
LNQAKGWLRDPSASPGDAGEQAIRQILDEAGKVGELCAGKERREILGTCKMLGQMTDQ  
VADLRARGQGSSPVAMQKAQQVSQGLDVLTAKVENAARKLEAMTNSKQSIKKIDAAQ  
NWLADPNGGPEGEEQIRGALAEARKIAELCDDPKERDDILRSIGEISALTSKLADLRR  
QGKGDSPEARALAKQVATALQNLQTKTNRAVANSRPAKAAVHLEGKIEQAQRWIDNPT  
VDDRGVGGQAAIRGLVAEGHRLANVMMGPYRQDLLAKCDRVDQLTAQLADLAARGESES  
PQARALASQLQDSLKDLKARMQEAMTQEVSDVFSDDTTPIKLLAVAATAPPDAPNREE  
VFDERAANFENHSGKLGATAEKAAAVGTANKSTVEGIQASVKTARELTPQVVSAARIL  
LRNPGNQAAAYEHFETMKNQWIDNVEKMTGLVDEAIDTKSLDASEEAIKKDLCKCKVA  
MANIQPQMLVAGATSIARRANRILLVAKREVENSEDPKFREAVKAASDELSTISPMV  
MDAKAVAGNISDPGLQKSFLDSGYRILGAVAKVREAFQPQEPDFPPPPPDLEQLRLTD  
ELAPPKPLPEGEVPPPRPPPEEKDEEFPEQKAGEVINQPMMAARQLHDEARKWSS  
KGNDIIAAAKRMALLMAEMSRLVRGGSGTKRALIQCAKDIKASDEVTRLAKEVAKQC  
TDKIRITNLLQVCERIPTISTQLKILSTVKATMLGRNTNISDEESEQATEMLVHNAQNL  
MQSVKETVREAEAAASIKIRTDAGFTLRWVRKTPWYQ

**Figure 24. (Page 4 of 46)****M90354 Basic Transcription Factor 3 Homologue**

1 aagcttttag ttccctttaa tcataaaagc cacttgctaa ctaaaactag agatagctca  
61 agctatctga ttttaaaggc ttagtctcaa tgtgtccctt ccctgaaatc ccagtagagt  
121 agccaattgt ctgaaacccg cttggattta gcaatgaaac acctcagtc tggccaaacc  
181 aagacagtgg gtctcaggaa acattctca tctaataaa ggcaaattaa ctacagttga  
241 cccttgaaca acatgggggt tatgggtgct gacttcccat gcagtaaaaa atctgggtat  
301 aactttcat tccacaaaaa ctttgcta atgccttaact gttactgga agcctacca  
361 ataacacata cagttgatta acacatatat tgtatgtatt atattacaat aaattaagct  
421 agagaaaaga aaatgtattc ctttgctgc catcctgcct ccctgtgtgc tttaatctc  
481 agctgtgtc acccgggact cccaagtgc caaccctagt cccacagca gcccttttc  
541 cactcagata agatgaaaga aacaatcatg aacaaaaac tcacaaacg gcaagcagaa  
601 gtgcacactg gtcggaaagg aactgctcac aggaaaaagg tggttcacag catctgagac  
661 gctgtgttg agggcaagta ggccccttg acaccttgg tgtgaactc atgaggttt  
721 gaatgtccag ggacattggc caatatcaaa agaactttaa aagtcagtt ggtaaggtag  
781 ttcttgactt cagggacaaa acagcaatgg aaccaatcca gaaaaagggt tctcattgtc  
841 caggccttct ggtacaacca aaagactggc agctggcatt tatctgtcc ctcaaggct  
901 cagagggttaa cggttttata cataagggtg gtcctgatca taaacctagc gacagcagag  
961 gataaaaaa ttcatgtctc cttaaagaaa ttaggggtta acaatatccc tggattgaa  
1021 gaggtgaata tgtttacaca ccaaggaaca gtgattcact ttaacaacc tgaagttcag  
1081 gcctcgtgg cagcaaacac tttaccatg acaggccatg ctgagacaaa gcagtgaca  
1141 gaaatgctac tcagcatcga tcataaacca gtgctgcaga tggctgact agttcaaaga  
1201 gactggctaa cactgcccac acaatctgtg ggtggaaaag caccattgc tactggagag  
1261 gatgatgaag ttctagatct tgtggagaat tctgatgagg ctccaacaa tgaggcaaac  
1321 tgaattaagt caactctga agaagataaa actgaagta gttactgaga gctgctgtt  
1381 tatgttatga ctgctttta aaaatgttt tgtttacaga tcttaataaa atctagatct  
1441 ctaatattt

Figure 24. (Page 5 of 46)

**J04111 Human c-jun proto oncogene**

1 cccggggagg ggaccgggga acagagggcc gagaggcgtg cggcaggggg gagggtagga  
 61 gaaagaaggg cccgactgta ggagggcagc ggagcattac ctcacccgt gagcctccgc  
 121 gggcccagag aagaatcttc tagggtggag tctccatggt gacgggcggg cccgcccccc  
 181 tgagagcgac gcgagccaat gggaaggcct tggggtgaca tcatgggcta ttttagggg  
 241 ttgactggta gcagataagt gttgagctcg ggctggataa gggctcagag ttgactgag  
 301 tgtggctgaa gcagcgaggc gggagtggag gtgcgaggag tcaggcagac agacagacac  
 361 agccagccag ccaggtcggc agtatagtcc gaactgcaaa tctattttc tttcacctt  
 421 ctctctaaact gccagagct agcgcctgtg gctcccgggc tgggtggttc ggagtgtcca  
 481 gagagccttg tctccagcgc gccccgggag gagagccctg ctgccaggc gctgttgaca  
 541 gcggcgga aa gcagcggtac cccacgcgc cggcggggga cgtcggcgag cggctgcage  
 601 agcaaagaac ttcccgggc gggaggaccg gagacaagtg gcagagtccc ggagcgaact  
 661 ttgcaagcc ttctctgct cttagcttc tccacggcgg taaagaccag aaggcggcgg  
 721 agagccacgc aagagaagaa ggacgtcgc tcagcttcgc tcgaccgggt tgttgaactt  
 781 gggcgagcgc gagccgcgc tgcggggcgc cccctcccc tagcagcga ggaggggaca  
 841 agtcgtcga gtccggcgg ccaagaccgc ccgcccggcg gccactgcag ggtccgcact  
 901 gatccgctcc gcggggagag ccgctgctct gggaagtgag ttgcctgcg gactccgagg  
 961 aaccgtcgc cccgaagagc gctcagttag taccgcgac tttaaaagc cgggtagcgc  
 1021 gcgcgagtcg acaagtaaga gtgcgggagg catcttaatt aacctgcgc tcctggagc  
 1081 gagctggtag ggaggcgca gcggggacga cagccagcgg gtgcgtgcgc tcttagagaa  
 1141 actttccctg tcaaaggctc cggggggcgc ggggtgtccc cgttgccag agccctgttg  
 1201 cggccccgaa acttgtgcgc gcacgcaaa ctaacctcac gtgaagtac ggactgttct  
 1261 atgactgaa agatggaac gacctctat gacgatgcc tcaacgcctc gttctccc  
 1321 tccgagagcg gaccttatgg ctacagtaac cccaagatcc tgaacagag catgaccctg  
 1381 aacctggccg acccagtgag gagcctgaag ccgcacctcc gcgccaagaa ctcggacctc  
 1441 ctcacctgc ccgacgtggg gctgctcaag ctggcgtcgc ccgagctgga gcgctgata  
 1501 atccagtcca gcaacgggca catcaccacc acgcccaccc ccaccagtt cctgtgccc  
 1561 aagaacgtga cagatgagca ggagggggtc cccgagggct tegtgcgcgc cctggccgaa  
 1621 ctgcacagcc agaacacgt gcccagcgtc acgtcggcgg cgcagccggt caacggggca  
 1681 ggcatggtag ctcgcgggt agcctcgggt gcagggggca gcggcagcgg cggctcagc  
 1741 gccagcctgc acagcgagcc gccggtctac gcaaacctca gcaactcaa cccaggcgcg  
 1801 ctgagcagcg gcggcggggc gccctctac ggcgcggcgg ccttgccct tccgcgcaa  
 1861 cccagcagc agcagcagcc gccgcaccac ctgccccagc agatgcccgt gcagcaccg  
 1921 cggctgcagg cctgaagga ggagcctcag acagtcccc agatgcccgg cgagacaccg  
 1981 cccctgtccc ccatgacat ggagtcccag gacgggatca aggcggagag gaagcgcag  
 2041 aggaaccgca tcgtgcctc caagtccga aaaaggaaagc tggagagaat cggccggctg  
 2101 gaggaaaaag tgaaaacctt gaaagctcag aactcggagc tggcgtccac ggccaacatg  
 2161 ctcagggaac aggtggcaca gcttaaacag aaagtcata accacgttaa cagtgggtgc  
 2221 caactcatgc taacgcagca gttgcaaca tttgaagag agaccgtcg gggctgaggg  
 2281 gcaacgaaga aaaaaataa cacagagaga cagacttgag aacttgaca gttgcgacgg  
 2341 agagaaaaaa gaagtgtccg agaactaaag ccaagggtat ccaagttgga ctgggttcgg  
 2401 tctgacggcg ccccgagtg gcacgagtgg gaaggacttg gtgcgcctt ccttggcgt  
 2461 ggagccaggg agcggccgc tgcgggctgc ccgctttgc ggacgggctg tcccgcgcg  
 2521 aacggaactg tggacttcg ttaacttga ccaagaactg catggacct acattcgatc  
 2581 tcttcagta ttaaggggg gagggggagg gggttcaaa ctgcaataga gactgtagat  
 2641 tgcttctgta gtactccta agaacacaaa gcggggggag ggttggggag gggcggcagg  
 2701 agggaggttt gtgagagcga ggctgagcct acagatgaac tcttctggc ctgcttctg  
 2761 taactgtgta tgcacatata tatattttt aatttgatta aagctgatta ctgtcaataa

**Figure 24. (Page 6 of 46)**

2821 acagcttcat gcctttgtaa gttatttctt gtttgttgt ttgggtatcc tgcccagtgt  
2881 tgtttgtaaa taagagattt ggagcactct gagttacca ttgtaataa agtatataat  
2941 tttttatgt ttgtttctg aaaattccag aaaggatatt taagaaaata caataaacta  
3001 ttggaaagta ctcccctaac ctctttctg catcatctgt agatcctagt ctatctaggt  
3061 ggagttgaaa gagttaagaa tgctcgataa aatcactctc agtgcttctt actattaagc  
3121 agtaaaaaact gttctctatt agacttagaa ataaatgtac ctgatgtacc tgatgctatg  
3181 tcaggettca tactccacgc tccccagcg tatctatatg gaattgctta ccaaaggcta  
3241 gtgcgatgtt tcaggaggct ggaggaaggg gggttgcagt ggagaggac agcccactga  
3301 gaagtc aaac atttcaaagt ttggattgca tcaagtggca tgtgctgtga ccatttataa  
3361 tgttagaaat ttacaatag gtgcttattc tcaaagcagg aattggtggc agattttaca  
3421 aaagatgtat ccttccaatt tggaatcttc tctttgacaa ttcttagata aaaagatggc  
3481 ctttgtctta tgaatattha taacagcatt ctgtcacaat aaatgtattc aaataccaat  
3541 aacagatctt gaattgcttc cctttactac tttttgttc ccaagttata tactgaagtt  
3601 tttattttta gttgctgagg tt

**Figure 24. (Page 7 of 46)****K00650 Human c-fos proto-oncogene**

1 gcaggaacag tgctagtatt gctcgagccc gagggctgga ggtagggga tgaaggctg  
 61 ctccacget ttgactgaa ttagggctag aattggggat gggggtaggg gcgcattcct  
 121 tggggagccg aggttaagt cctcggggtc ctgtactga tgcgtttct cctatctctg  
 181 agcctcagaa ctgtctcag ttccgtaca agggtaaaaa ggcgtctct gccccatccc  
 241 ccccgacctc gggaacaagg gtccgcattg aaccagggtc gaatgtctc tctcattctg  
 301 cgccgtccc gcctcccctc ccccgccgc ggccccgcc tcccccgca ctgcaccctc  
 361 ggtgttgct gcagcccgcg agcagttccc gtcaatccct cccccctac acaggatgtc  
 421 catattagga catctgcgc agcaggttc cacggcctt cctgtagcc ctggggggag  
 481 ccatccccga aacctcctat ctgggggggc ccacgagacc tctgagacag gaactgcgaa  
 541 atgtcacga gattaggaca cgcgccaagg cgggggcagg gagctgcgag cgctggggac  
 601 gcagccgggc ggccgcagaa gcgcccaggc ccgcgcgcca cccctctggc gccaccgtgg  
 661 ttgagcccg gacgtttaca ctattcata aaacgttgt tataaaagca gtggtgcgg  
 721 cgcctctac tccaaccga tctgcagca gcaactgaga agccaagact gagccggcgg  
 781 ccgcgccgca gcgaacgagc agtgaccgtg ctctaccca gctctgttc acagcgcca  
 841 cctgtctcg cccctcgcc cctcgccgg cttgcctaa ccgccacgat gatgtctcg  
 901 ggcttcaacg cagactcga ggcgtcatc tcccgctga gcagcgcgc cccggccggg  
 961 gatagcctc ctactacca ctacccgca gactcctct ccagcatggg ctgcctgtc  
 1021 aacgcgcagg taaggctggc tcccgtcg cgcggggcgg ggggcttggg gtcgcggagg  
 1081 aggagacacc ggccgggacg ctccagtaga tgagtagggg gctccctgt gcctggaggg  
 1141 aggtgccgt ggccggagcg gtgcccgtc gggggctcgg gacttgcct gagcgcacgc  
 1201 acgttgcca tagtaagaat tggttcccc ttcgggaggc aggttcgtc tgagcaacct  
 1261 ctggtctga ctccaggacg gatctctgac attagctgga gcagacgtg cccaagcaca  
 1321 aactcgtaa ctagagcctg gcttctcgg ggagggtgga gaaagcggca atccccctc  
 1381 ccccgccagc ctggagcagc gagggaggat gagggaggag ggtgcagcgg gcgggtgtgt  
 1441 aaggcagttt cattgataaa aagcgagttc attctggaga ctccggagcg gcgctgcgt  
 1501 cagcgagac gtcagggata ttataacaa acccccttc aagcaagtga tgctgaaggg  
 1561 ataacgggaa cgcagcggca ggatggaaga gacaggcact gcgtgcgga atgcctggga  
 1621 ggaaaagggg gagaccttc atccaggatg agggacattt aagatgaaat gtccgtggca  
 1681 ggatcgttc tcttactgc tgcagcggc actgggaact cgcaccacct gtgtccgga  
 1741 cctgctcgt cagtcgggt tccccctt gtttgttct aggactctg cacggacctg  
 1801 gccgtctca gtgccaaatt cattcccacg gtcactgcca tctgaccag tccggacctg  
 1861 cagtggctgg tgcagccgc cctgctctc tctgtgccc catcgagac cagagccct  
 1921 cacccttgc gagtccccgc cccctcgtc ggggcttact ccagggtgg cgttgtgaag  
 1981 accatgacag gagcccgagc gcagagcatt ggcaggaggg gcaagggtga acaggtagg  
 2041 aactctagcg tactcttct gggaatgtg ggcctgggtg ggaagcagcc ccggagatgc  
 2101 aggagcccag tacagaggat gaagccactg atggggctgg ctgcacatc gtaactggga  
 2161 gccctggctc caagccatt ccatccaac tcagactctg agtctaccc taagaagtac  
 2221 tctcatagt ttctccctaa gtttctacc gcatgcttc agactgggtc ctctttgtt  
 2281 ctcttctga ggatcttatt ttaatgcaa gtcacaccta tctgcaact gcaggtcaga  
 2341 aatggtttca cagtggggtg ccaggaagca gggaagctgc aggagccagt tctactggg  
 2401 tgggtgaatg gaggtgatg cagacattt tactgaatg cgtctttt ttgtgattat  
 2461 tctagttatc tccagaagaa gaagagaaaa ggagaatccg aagggaagg aataagatgg  
 2521 ctgcagccaa atcccgaac cggaggaggg agctgactga tacactcaa gcggtaggt  
 2581 ctctgtgggt tctcctttt taaacttaa gggaaagtt gagattgagc ataaggccc  
 2641 ttgagtaaga ctgtgtctta tcttctct taccctctg tatacaggag acagaccaac  
 2701 tagaagatga gaagtctgt ttgcagaccg agattgcaa cctgtgaag gagaaggaaa  
 2761 aactagagtt catcctggca gtcaccgac ctgcctgca gatccctgat gacctgggt

**Figure 24. (Page 8 of 46)**

2821 tcccagaaga gatgtctgtg gcttcccttg atctgactgg gggcctgcc a gaggttgcc a  
 2881 ccccgagtc tgaggaggcc ttaccctgc ctctcctcaa tgaccctgag cccaagccct  
 2941 cagtggaaacc tgtcaagagc atcagcagca tggagctgaa gaccgagccc ttgatgact  
 3001 tcctgttccc agcatcatcc agggccagtg gctctgagac agcccgtcc gtgccagaca  
 3061 tggacctatc tgggtccttc tatgcagcag actgggagcc tctgcacagt ggctccctgg  
 3121 ggatggggcc catggccaca gagctggagc ccctgtgcac tccggtggtc acctgtactc  
 3181 ccagctgcac tggttacacg tcttcttcg tcttcaccta ccccgaggct gactcctcc  
 3241 ccagctgtgc agctgcccac cgcaagggca gcagcagcaa tgagccttcc tctgactcgc  
 3301 tcagctcacc cacgtgctg gcctgtgag ggggcaggga aggggaggca gccggcaccc  
 3361 acaagtgcc a tccccgagc tgggtcatta cagagaggag aaacacatct tcctagagg  
 3421 gttcctgtag acctagggag gacctatct gtgcgtgaaa cacaccaggc tgtgggcctc  
 3481 aaggactga aagcatccat gtgtggactc aagtccttac ctctccgga gatgtagcaa  
 3541 aacgcatgga gtgtgtattg ttccagtga cacttcagag agctggtagt tagtagcatg  
 3601 ttgagccagg cctgggtctg tgtctcttt ctcttctcc ttgtctct catagcatta  
 3661 actaatctat tgggttcatt attgaatta acctggtgct ggatatttc aaattgtatc  
 3721 tagtgcagct gattttaaca ataactactg tgttctggc aatagtgtgt tctgattaga  
 3781 aatgaccaat attatactaa gaaaagatac gactttatt tctggtagat agaaaataat  
 3841 agctataacc atgtactgta gttttcttc aacatcaatg ttcattgtaa tgttactgat  
 3901 catgcattgt tgagggtgct tgaatgtct gacattaaca gttttccatg aaaacgttt  
 3961 attgtgttt taatttattt attaatgag attctcagat atttatatt ttattttat  
 4021 ttttctacc ttgaggtcct ttgacatgtg gaaagtgaat tgaatgaaa aatttaagca  
 4081 ttgtttgctt attgttcaa gacattgtca ataaaagcat ttaagttaa tgcgaccaac  
 4141 ctgtgctct ttcattctg gaagtctgt aagttctga aaggtattat tggagaccag  
 4201 ttgtcaaga aggttagctg ctggaggggg acacaccctc tgtctgatcc ctatcaaaag  
 4261 aggacaagga aactatagag ctgattttag aatattttac aaatacatgc ctccattgg  
 4321 aatgctaaga tttctactg ctctgggga cggggaaaccg ctgtgtaaca gctttgtgg  
 4381 gaatacattt tttctgttc agtactcgca gggggaaata ttaaatttt gttgtgctaa  
 4441 tattaatc agatgtttg atcttaaagg aaccctttaa gcaaacagaa cctagctttg  
 4501 tacagactat ttaactttt tttctcaca aaatcacgtg gagggttatt ctactcaaa  
 4561 gatgagcaaa tgaagaatg gtagaataa acaactttct tgatattccg ttatcggcac  
 4621 tagaatctc ctgctcgta tctatccag caggctgaac tgcctctga tacttggtta  
 4681 aaaaaaatt tcaggccggg cgcggtggcc catgcctgta atcctagcac ttgggaggc  
 4741 cgaggcaggc ggatcacctg aggtcgggag ttcgagacca gcctgacca catggagaaa  
 4801 ccccgcttt actaaaaata caaaattagc ctggtgtggt ggtgcatgcc tgaatccta  
 4861 gctacttgag aggtgagac aggaaaatca ctgaactcg ggaggcggat gttgcagcga  
 4921 actgagattg cgccattgca ctccagcctg ggcaacaaga ttgaaactct gtttaaaaaa  
 4981 aaaagtttc actaatgtgt acatttttt gtactctttt attctcgaag gggaaggagg  
 5041 gctattgccc tatcccttat taataaatgc attgtggtt ctgtttctc taataccata  
 5101 tgcccttcat tcagtttata gtggcgaggaa gtgggggaga aaaagtgtct cagaaatcaa  
 5161 aagatatctc aaacagcaca aataatggct gatcgttctg caaacaaaaa gttacataat  
 5221 agctcaagaa ggagaagtca acatgactct gaacaagctt taacttagaa actttatcat  
 5281 ctaagggaag aacgtgacct ttgtccagga cgtctctggt aatggggcac ttacacacac  
 5341 atgcacacgt acaaacacaca gggaaaggag accgcccctc tgcctctgct cgcgagtac  
 5401 acgcaggcac catgcactat gtttcacac aactgggtg gaagaagagc ttcagcgcca  
 5461 gtcttcta at gcttgggtga taatgaaaat cactgggtgc ttatggggtg tcatattcaa  
 5521 tcgagttaaa agttttaatt caaatgaca gttttactga ggtgatgtt ctgtctatg  
 5581 atatctctgc cctcccata aaaaatggaca tttaaaagca acttaccgct cttagatca  
 5641 ctctatatc acacaccact tgggtgtctg tttctgtag acttgtgatg acagtggcct  
 5701 taggatccct gtttctgtt caaagggcaa atattttata gcctttaat atacctaac

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5761 taaatacaga attaataaa ctaacaaca cctggtctga aataacaagg tgatctacc  
5821 tggaaggaaac ccagctgggtg ggccaggagc ggtggctcac acctgtaatt ccagcactt  
5881 gggaggctga gacaggagga tcttggtggt ccaggagttt gagaccagcc tgggcaacat  
5941 ggcaaaaccc agtgtgcttc tgtgtccca gctacactac tcaggaggct gaggcaggag  
6001 tatgactga gcctgggagg gggagggtgc agagaactga tattgcacca ccactgcact  
6061 ccagcctggg tgacacagca aaacctatc tcaaaaaaa aaaaaaaaaa aaggaaacca  
6121 gctggttct gtaggtgtgc aataataaca accagaggaa gaaaaggaag acgattccc  
6181 agatgaagaa gggcagctgg accttcggac

**Figure 24. (Page 10 of 46)****NM 080422 Homo Sapiens Protein Tyrosine Phosphatase, non-receptor type 2**

1 gctcgggcg cagctctgcg cgctgacgtc cgacgtcca ggtacttcc ccacggccga  
61 cagggcttgg cgtgggggcg gggcgcgcg cgacgcgcgc atcgcccgca gcgccagcgc  
121 tctccccgga tcgtgcgggg cctgagcctc tccgccggcg caggctctgc tcgcgccagc  
181 tcgctcccg agccatgcc accaccatcg agcgggagtt cgaagagttg gatactcagc  
241 gtcgctggca gccgctgtac ttggaatc gaaatgagtc ccatgactat cctcatagag  
301 tggccaagtt tccagaaaac agaaatcgaa acagatacag agatgtaagc ccatatgac  
361 acagtcgtgt taaactgcaa aatgctgaga atgattatat taatgccagt ttagtgtaca  
421 tagaagaggc acaaaggagt tacatctaa cacagggtcc acttcctaac acatgctgcc  
481 attctggct tatggttgg cagcagaaga ccaaagcagt tgtcatgctg aaccgcattg  
541 tggagaaaga atcggttaaa tgtgcacagt actggccaac agatgaccaa gagatgctgt  
601 ttaagaaac aggattcagt gtgaagctct tgcagaaga tgtgaagtcg tattatacag  
661 tacatctact acaattagaa aatatcaata gtggtgaaac cagaacaata tctcacttc  
721 attatactac ctggccagat ttggagtc ctgaatcacc agcttcattt ctcaattct  
781 tgtttaaagt gagagaatct ggctcctga accctgacca tgggcctgcg gtgatccact  
841 gtagtgagg cattgggcg tctggcacct tctctctgt agacactgt cttgtttga  
901 tggaaaaagg agatgatatt aacataaac aagtgttact gaacatgaga aaataccgaa  
961 tgggtcttat tcagacccca gatcaactga gattctcata catggctata atagaaggag  
1021 caaatgtat aaaggagat tctagtatac agaaacgatg gaaagaactt tctaaggag  
1081 acttatctcc tgccttggat cattcaccaa acaaaataat gactgaaaa tacaatgga  
1141 acagaatagg tctagaaga gaaaaactga caggtgaccg atgtacagga cttctctta  
1201 aaatgcaaga tacaatggag gagaacagt agagtgtct acggaaacgt attcgagagg  
1261 acagaaaggc caccacagct cagaagggtc agcagatga acagaggcta aatgagaatg  
1321 aacgaaaaag aaaaaggcca agattgacag acacctaata tcatgactt gagaatattc  
1381 tgcagctata aatttgaac cattgatgtg caaagcaaga cctgaagccc actccggaaa  
1441 ctaaagttag gctcgctaac cctctagatt gcctcacagt tgtttgtta caaagtaaac  
1501 ttacatcca ggggatgaag agcaccacc agcagaagac ttgcagaac ctttaattgg  
1561 atgtgttaag tgttttaaat gtagttaga aatgtagaaa gatgtacaag aaataaatta  
1621 ggagagatta cttgtattg tactgccatt cctactgtat tttatactt ttggcgaca  
1681 ttaaatattt ttgttaata aaaaaaaaaa aaaa



**Figure 24. (Page 11 of 46)****M68520 Human cdc2-related protein kinase**

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1 ggagggcgca acattgttc aagttggcca aattgacaag agcgagaggt atactgcgtt
61 ccattccgac cggggccacg gtactgggcc ctgtttcccc ctctcggcc cccgagagcc
121 agggctccgc ttctgcaggg tccccaggcc cccgctccag ggccgggctg acccgactcg
181 ctggcgcttc atggagaact tccaaaaggt ggaaaagatc ggagagggca cgtacggagt
241 tgtgtacaaa gccagaaaca agttgacggg agaggtgggt gcgcttaaga aaatccgcct
301 ggacactgag actgaggggtg tgcccagtac tgccatccga gagatctctc tgcttaagga
361 gcttaacat cctaatttg tcaagctgct ggatgtcatt cacacagaaa ataaactcta
421 cctggttttt gaattctgc accaagatct caagaaatc atggatgcct ctgctctcac
481 tggcattcct ctccccca tcaagagcta tctgtccag ctgctccagg gcctagcttt
541 ctgccattct catcgggtcc tcaccgaga ccttaacct cagaatctgc ttattaacac
601 agagggggcc atcaagctag cagactttgg actagccaga gcttttgag tcctgttctg
661 tacttacacc catgaggtgg tgacctgtg gtaccgagct cctgaaatcc tcctgggctg
721 caaatattat tccacagctg tggacatctg gagcctgggc tgcatctttg ctgagatggt
781 gactcgccgg gccctattcc ctggagattc tgagattgac cagctcttcc ggatctttcg
841 gactctgggg accccagatg aggtgggtgt gccaggagt acttctatgc ctgattacaa
901 gccaaagttc ccaagtggg cccggcaaga ttttagtaaa gttgtacctc cctgggatga
961 agatggacgg agcttggtat cgcaaatgct gcactacgac ctaacaagc ggatttcggc
1021 caaggcagcc ctggctcacc ctttctcca ggatgtgacc aagccagtac ccatctctcg
1081 actctgatag ccttcttgaa gccccagcc ctaatctcac cctctcctcc agtgtgggct
1141 tgaccaggct tgcgctggg ctatttgac tcaggtgggc cctctgaact tgcctaaac
1201 actcaccttc tagtcttggc cagccaactc tgggaatata ggggtgaaag gggggaacca
1261 gtgaaaatga aaggaagttt cagtattaga tgcacttaag ttagcctcca ccacccttc
1321 ccccttctct tagttattgc tgaagagggt tggataaaaa ataattttaa aaaagccttc
1381 ctacacgtta gatttgccgt accaatctct gaatgcccc taattattat ttccagtgt
1441 tgggatgacc aggatcccaa gcctcctgct gccacaatgt ttataaagc caaatgatag
1501 cgggggctaa gttggtgctt ttgagaacca agtaaaaca aaccactggg aggagtctat
1561 tttaagaat tcggttgaaa aaaatagatc caatcagttt ataccctagt tagtgttttg
1621 cctcacctaa taggctggga gactgaagac tcagcccggg tggctgcaga aaaatgattg
1681 gcccagctcc cctgtttgt ccttctaca ggcatgagga atctgggagg ccttgagaca
1741 gggattgtgc ttattccaa tctattgctt caccatggcc ttatgaggca ggtgagagat
1801 gtttgaattt ttcttctct ttagtattc ttagtgttc agttgccaag gatccctgat
1861 cccatttcc tetgacgtcc acctcctacc ccataggagt tagaagttag ggtttaggca
1921 tcattttgag aatgctgaca cttttcagg gctgtgattg agtgagggca tgggtaaaaa
1981 tatttcttta aaagaaggat gaacaattat atttatattt caggttatat ccaatagtag
2041 agttggcttt tttttttt ttttggtcat agtgggtgga ttgttgcca tgtgcacctt
2101 ggggtttgtt aatgacagtg ctaaaaaaaa agcatttttt tttatgatt tgtctctgtc
2161 acccttgccc ttgagtgtc ttgctattaa cgttattgt aatttagttt gta

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**Figure 24. (Page 12 of 46)****M74091 Human Cyclin C**

1 gagcgcgggt accggacggg ctgggtctat ggctgctccg cggccgctcc gccgcgtggt  
61 gctttttat cagggcaagc tgtgttccat ggcagggaac ttttggcaga gctcccacta  
121 ttgcaatgg attttgata aacaagatct gttgaaggag cgccaaaagg atttaaagtt  
181 tcttcagag gaagaatatt ggaagtaca aatattttt acaaatgtta tccaagcatt  
241 aggtgaacat cttaaataa gacaacaagt tattgccact gctacggtat attcaagag  
301 attctatgcc aggtattctc tgaaaagtat agatcctgta ttaatggctc ctacatgtgt  
361 gttttggca tccaaagtag aggaatttg agtagttca aatacaagat tgattgctgc  
421 tgctacttct gtattaaaaa ctagatttc atatgcctt ccaaaggaat ttccttatag  
481 gatgaatcat atattagaat gtgaattcta tctgttagaa ctaatggatt gttgcttgat  
541 agtgtatcat ccttatagac ctttgctcca gtatgtgcag gacatgggcc aagaagacat  
601 gttgctccc ctgcatgga ggatagtga tgatacctac agaacggatc ttgcctact  
661 gtatcctct tcatgatag ctttagctg cctacatgta gcctgtgttg tacagcagaa  
721 agatgccagg caatggttg ctgagcttc tgtggatatg gaaaagattt tggaaataat  
781 cagggttatt taaaactat atgagcagt gaagaattc gatgagagaa aagagatggc  
841 aaccattctt agtaagatgc caaaaccaa accacctcca aacagtgaag gagagcaggg  
901 tccaaatgga agtcagaact ctagctacag ccaatctaa aacattccga agaattccat  
961 agtggaccac ttggaataa accattggac agatttcagt aatgtcttca gtggaacaca  
1021 aatgaaaatg aatagcttgt ttctgtcaag catattggaa agtgatttta ttttgcaa  
1081 tagttttct ttaatatgat tctagtacat aattgattga taaatctct tgattataa  
1141 tgtttgaaa ggttctaagg ggacctacag acagacatac atagacattt caaaattaat  
1201 agcttttgat tagtataata ttcttaatt tggataataa aaattgtagc tttttattaa  
1261 gccaggaaac atgaagcata atttgttta aattctctt ggtcattgag ggacaaaaa  
1321 aggacgtaaa atttacagtc aatctatgag ggttttttc cctccataag ttaacttta  
1381 aaactgtatt taaggaatca aatcttaca aatcctggaa gattttgga atgatgtga  
1441 taatttcagg gaaattaatc aagtaccgta tattgattta aaagtgtatt ttattcagta  
1501 gtttgagg

**Figure 24. (Page 13 of 46)****U60325 Human DNA polymerase gamma**

1 aggatttggg gtggaaggca ggcattgtca acccatgtca ctgacaggag agcagagaca  
 61 gacgtgtctc tctccacgtc ttccagccag taaaagaagc caagctggag cccaaagcca  
 121 ggtgttctga ctcccagcgt ggggggtccct gcaccaacca tgagccgcct gctctggagg  
 181 aaggtggccg gcgccaccgt cgggccaggg ccggttcag ctccggggcg ctgggtctcc  
 241 agtcccgccc ccgcgtccga cccagcgcac gggcagcggc ggcggcagca gcagcagcag  
 301 cagcagcagc agcagcaaca gcagcctcag cagccgcaag tgctatctc ggaggcgagg  
 361 cagctgcggc acaaccatt ggacatccag atgctctcga gagggtgca cgagcaaatc  
 421 ttcgggcaag gaggggagat gcctggcgag gccgcggtgc gccgcagcgt cgagcacctg  
 481 cagaagcagc ggctctgggg gcagccagcc gtgcccttgc ccgacgtgga gctgcgctg  
 541 ccgcccctct acgggggaca cctggaccag cacttccgcc tctggccca gaagcagagc  
 601 ctgccctacc tggaggcggc caacttgctg ttgcaggccc agctgcccc gaagccccg  
 661 gcttgggcct gggcggaggg ctggaccggg tacggcccc agggggaggc cgtaccctg  
 721 gccatcccc aggagcgggc cctggtgttc gacgtggagg tctgcttggc agagggaact  
 781 tgccccacat tggcgggtggc catatcccc tcggcctggt attcctggtg cagccagcgg  
 841 ctggtggaag agcgttactc ttggaccagc cagctgtcgc cggctgacct catccccctg  
 901 gaggtcccta ctggtgccag cagccccacc cagagagact ggcaggagca gttagtgtg  
 961 gggcacaatg tttccttga ccgagctcat atcagggagc agtacctgat ccagggttcc  
 1021 cgcattgcgt tcttgacac catgagcatg cacatggcca tctcagggt aagcagcttc  
 1081 cagcgcagtc tgtggatagc agccaagcag ggcaaacaca aggtccagcc ccccaaaag  
 1141 caaggccaga agtcccagag gaaagccaga agaggcccag cgatctcatc ctgggactgg  
 1201 ctggacatca gcagtgtcaa cagtctggca gaggtgcaca gactttatgt aggggggcct  
 1261 cccttagaga aggagcctcg agaactgtt gtgaagggca ccatgaagga cattcgtgag  
 1321 aactccagg acctgatgca gtactgtcc caggacgtgt gggccacca tgaggtttc  
 1381 cagcagcagc taccgtctt ctggagagg tgccccacc cagtactct gcccgcatg  
 1441 ctggagatgg gtgtctcta cctgcctgtc aaccagaact gggagcgta cctggcagag  
 1501 gcacagggca cttatagga gctccagcg gagatgaaga agtcgttgat ggtatggcc  
 1561 aatgatgect gccagctgt ctacggagag aggtacaaag aagaccctg gctctgggac  
 1621 ctggagtggg acctgcaaga atttaagcag aagaaagta agaagggtga gaaggaacca  
 1681 gccacagcca gcaagttgcc catcgagggg gctggggccc ctggtgatcc catggatcag  
 1741 gaagacctcg gccccgcag tgaggaggag gagtttcaac aagatgtcat gggccgcgc  
 1801 tgcttgcaag agctgaagg gaccacagag ctctgcccc agcgccccca gcaccttct  
 1861 ggacacctg gatggtacc gaagctctgc ccccggttag acgacctgc atggacccg  
 1921 ggccccagcc tctcagcct gcagatcgg gtcacaccta aactcatggc acttacctg  
 1981 gatggttcc ctctgacta ctacagcgt catggttgg gctacttgg cctggggcg  
 2041 cgggacaacc tggccaagct gccgacagg accaccctgg agtcagctg ggtggtctg  
 2101 ccctacagag ccatcgagtc cctgtacagg aagcactgtc tcgaacagg gaagcagcag  
 2161 ctgatgccc aggaggccg cctggcgagg gagttctgc tactgacaa tagtgccata  
 2221 tggcaaacgg tagaagaact ggattacta gaagtggagg ctgaggccaa gatggagaac  
 2281 ttgcgagctg cagtgccagg tcaacccta gctctgactg cccgtggtgg cccaaggac  
 2341 acccagccca gctatcaca tggcaatgga ccttacaac acgtggacat ccttggtgc  
 2401 tggttttca agctgctca caaggatgt aatagctgt atgtgggaag cccctttgc  
 2461 aaggacttcc tgcccaagat ggaggtggc accctgcagg ctggcccagg aggtgccagt  
 2521 gggccccgtg ctctggaaat caacaaaatg attctttct ggaggaaag ccataaacg  
 2581 atcagctccc agatggtggt gtggtgccc aggtcagctc tgccccgtgc tgtatcagg  
 2641 caccctgact atgatagga aggcctctat ggggccatcc tgcccaagt ggtgactgc  
 2701 ggcacatca ctgcggggc tgggagccc acatggtca ccgccagca tgcccgccct  
 2761 gaccgagtag gcagtgaagt gaaagccatg gtgcaggccc cacctggcta caccctgtg

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2821 ggtgctgatg tggactccca agagctgtgg attgcagctg tgcttgaga cgccacttt  
2881 gccggcatgc atggctgcac agcctttggg tggatgacac tgcagggcag gaagagcagg  
2941 ggcactgac tacacagtaa gacagccact actgtgggca tcagccgtga gcatgccaaa  
3001 atctcaact acggccgcat ctatggtgct gggcagccct ttgctgagcg ctactaatg  
3061 cagttaacc accggctcac acagcaggag gcagctgaga aggcccagca gatgtacgt  
3121 gccaccaagg gcctccgctg gtatcggctg tcgcatgagg gcgagtggct ggtgagggag  
3181 ttgaacctcc cagtggacag gactgagggt ggctggattt ccctgcagga tctgcgcaag  
3241 gtccagagag aaactgcaag gaagtcacag tggagaagt gggaggtggt tgctgaacgg  
3301 gcatggaagg ggggcacaga gtcagaaatg tcaataagc ttgagagcat tgctacgtct  
3361 gacataccac gtaccccggt gctgggctgc tgcacagcc gagccctgga gccctcggct  
3421 gtccaggaag agtttatgac cagccgtgtg aattgggtgg tacagagctc tgctgtgac  
3481 tacttacacc tcatgctgtt ggccatgaag tggctgttg aagagttgc catagatggg  
3541 cgcttctgca tcagcatcca tgacgaggtt cgctacctgg tgcgggagga ggaccgtac  
3601 cgcgctgccc tggccttgca gatcaccaac ctcttgacca ggtgcatgtt tgcctacaag  
3661 ctgggtctga atgactgcc ccagtcagtc gccttttca gtgcagtcga tattgaccgg  
3721 tgcctcagga aggaagtgac catggattgt aaaaccctt ccaaccaac tgggatggaa  
3781 aggagatacg ggattccca ggggtgaagcg ctggatattt accagataat tgaactacc  
3841 aaaggctcct tggaaaaacg aagccagcct ggaccatagc actgcctgga ggctctgtat  
3901 ttgctccgtt ggagcttcat cgggggtgtg caggctccca aactcaggct tcagctgtg  
3961 cttttgcaa aagggttgc taaggccagc cattttcag tagcaggacc tgccaagaag  
4021 attccttcta actgaagggtg cagttgaatt cagtgggttc agaaccaaga tgccaacatc  
4081 ggtgtggact acaggacaag gggcattgtt gcttgttggg taaaaatgaa gcagaagccc  
4141 caaagttcac attaaactcag gcatttcatt ttttttcc ttttctctt ggctggttct  
4201 ttgtctgtc ccccatgctc tgatgcagtg ccctagaagg ggaaagaatt aatgctctaa  
4261 cgtgataaac ctgctccaag gcagtggaaa taaaaagaag gaaaaaaaaa aaaaaaaaaa

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**X52479 Protein Kinase C alpha**

1 ggagcaagag gtggttgggg ggggacatg gctgacgtt tcccgggcaa cgactccacg  
 61 gcgtctcagg acgtggccaa ccgcttcgcc cgcaaagggg cgctgaggca gaagaacgtg  
 121 cagcaggtga aggaccacaa attcatcgcg cgcttctca agcagccac cttctgcagc  
 181 cactgcaccg acttcatctg ggggtttggg aaacaaggct tccagtgcc agtttgctgt  
 241 tttgtgtcc acaagagggtg ccatgaattt gttactttt ctgtccggg tgcggataag  
 301 ggacccgaca ctgatgaccc caggagcaag cacaagtca aaatccacac ttacggaagc  
 361 cccaccttct gcgatcactg tgggtcactg ctctatggac ttatccatca agggatgaaa  
 421 tgtgacacct gcgatatgaa cggtcacaag caatgcgtca tcaatgtccc cagcctctgc  
 481 ggaatggatc acactgagaa gagggggcgg atttacctaa aggcctgaggt tgctgatgaa  
 541 aagctccatg tcacagtacg agatgcaaaa aatctaatac ctatggatcc aaacgggctt  
 601 tcagatcctt atgtgaagct gaaacttatt cctgatccca agaataaag caagcaaaaa  
 661 accaaaacca tccgtccac actaaatccg cagtggaatg agtcctttac attcaaattg  
 721 aaaccttcag acaagaccg acgactgtct gtgaaatct gggactggga tcgaacaaca  
 781 aggaatgact tcatgggac ctttctctt ggagtttcgg agctgatgaa gatccggcc  
 841 agtggatggt acaagttgct taaccaagaa gaaggtgagt actacaacgt accattccg  
 901 gaaggggacg aggaaggaaa catggaactc aggcagaaat tcgagaaagc caaacttggc  
 961 cctgctggca acaaagtcac cagtccctct gaagacagga aacaaccttc caacaacctt  
 1021 gaccgagtga aactcacgga ctcaatttc ctcatggtgt tgggaaaggg gagttttgga  
 1081 aaggtgatgc ttccgacag gaagggcaca gaagaactgt atgcaatcaa aatcctgaag  
 1141 aaggatgtgg tgattcagga tgatgacgtg gactgcacca tggtagaaaa gcgagtcttg  
 1201 gccctgcttg acaaaccccc gttcttgacg cagctgcaact cctgcttcca gacagtggat  
 1261 cggctgtact tcgtcatgga atatgtcaac ggtggggacc tcattgacca cattcagcaa  
 1321 gtaggaaaat ttaaggaaac acaagcagta ttctatgcgg cagagatttc catcggttg  
 1381 ttctttcttc ataaaagagg aatcatttat agggatctga agttagataa cgtcatgttg  
 1441 gattcagaag gacatatcaa aattgctgac ttgggatgt gcaaggaaaca catgatggat  
 1501 ggagtcacga ccaggacctt ctgtgggact ccagattata tcgccccaga gataatcgct  
 1561 tatcagccgt atggaaaatc tgtggactgg tgggcctatg gcgtcctgtt gtatgaaatg  
 1621 cttgccgggc agcctccatt tgatggtgaa gatgaagacg agctatttca gtctatcatg  
 1681 gagcacaacg ttctctatcc aaaatccttg tccaaggagg ctgtttctat ctgcaaagga  
 1741 ctgatgacca aacaccagc caagcggctg ggctgtgggc ctgaggggga gagggacgtg  
 1801 agagagcatg ccttcttcg gaggatcgac tgggaaaaac tggagaacag ggagatccag  
 1861 ccaccattca agcccaaagt gtgtggcaaa ggagcagaga actttgacaa gttcttcaca  
 1921 cgaggacagc ccgtcttaac accacctgat cagctggtta ttgctaacaat agaccagtct  
 1981 gattttgaag ggttctcgta tgcaacccc cagtttgc acccatctt acagagtgc  
 2041 gtatgaaact caccagcgag aacaaacacc tcccagccc ccagccctcc ccgcagtgga  
 2101 agtgaatcct taacctaaa attttaaggc cagggcttgt gtctgattcc atatggaggc  
 2161 ctgaaaattg tagggttatt agtccaaatg tgatcaactg ttcagggtct ctctcttaca  
 2221 accaagaaca ttatcttagt ggaag

**Figure 24. (Page 16 of 46)****D00017 Lipocortin II/Annexin A2**

1 catttgggga cgctctcagc tctcggcgca cggcccagct tccttcaaaa tgtctactgt  
61 tcacgaaatc ctgtgcaagc tcagcttgga gggatgacac tctacacccc caagtgcata  
121 tgggtctgtc aaagcctata ctaacttga tgctgagcgg gatgcttga acattgaaac  
181 agccatcaag accaaagggt tggatgaggt caccattgtc aacatttga ccaaccgcag  
241 caatgcacag agacaggata ttgccttcgc ctaccagaga aggacaaaa aggaacttgc  
301 atcagcactg aagtcagcct tatctggcca cctggagacg gtgatttgg gcctattgaa  
361 gacacctgtc cagtatgacg cttctgagct aaaagcttc atgaaggggc tgggaaccga  
421 cgaggactct ctattgaga tcactgtc cagaaccaac caggagctgc aggaaattaa  
481 cagagtctac aaggaaatgt acaagactga tctggagaag gacattatt cggacacatc  
541 tggtagcttc cgcaagctga tggttgccct ggcaaagggt agaagagcag aggatggctc  
601 tgcattgat tatgaactga ttgaccaaga tgctcgggat ctctatgacg ctggagtga  
661 gaggaagga actgatgttc ccaagtggat cagcatcatg accgagcggga gcgtgcccc  
721 cctccagaaa gtatttgata ggtacaagag ttacagccct tatgacatgt tggaaagcat  
781 caggaaagag gtaaaaggag acctggaaaa tgcttcctg aacctgggtc agtgcattca  
841 gaacaagccc ctgtattttg ctgatcggct gtatgactcc atgaagggca aggggacgcg  
901 agataaggct ctgatcagaa tcattgtctc ccgcagtga gtggacatgt tgaataatag  
961 gtctgaattc aagagaaagt acggcaagtc cctgtactat tatatccagc aagacactaa  
1021 gggcgactac cagaaagcgc tgctgtacct gtgtggtgga gatgactgaa gcccgcacag  
1081 gcctgagcgt ccagaaatgg tgctcaccat gctccagct aacagggtca gaaaaccagc  
1141 ttgcgaataa cagtcctcgt ggccatccct gtgagggtga cgttagcatt accccaacc  
1201 tcattttagt tgctaagca ttgcctggcc ttctgtcta gtctctctg taagccaaag  
1261 aaatgaacat tccaaggagt tggaaagtga gtctatgat tgaacactt gcctcctgt  
1321 gtactgtgtc ataaacagat gaataaactg aattgtact tt

**Figure 24. (Page 17 of 46)****AF531293 Histone H2b, member R**

1 aagagcgagt cttggcctta gcgcgggctt tgcctccctg cttgccacgt ccagacatag  
61 cgagcgcaac tcactacgag caaccacaaa gtgaacggga aaggcggcgc ttttataaa  
121 cactattggg cgcgaaaaag aagacgtgtt gttggtagg gctgcagttt aattcaacc  
181 aatagtagtg cgtcttctgg atttgcgaat cctgattggg cagacctgac ctctgacgtt  
241 accctgaata actaccaatc agacacaaga cttcaactct tcacctatt tgcataagcg  
301 attctatata aaagcgccct gtcataccct gtcacgctg ttttcctt tcgttggcgc  
361 tttatagcta cacagtgcta tgccagagcc agcgaagtct gctcccggcc cgaaaaaggg  
421 ctccaagaag gcggtgacta aggcgcagaa gaaagacggc aagaagcgca agcgcagccg  
481 caaggagagc tattccatct atgtgtacaa ggttctgaag caggctccacc ctgacaccgg  
541 catttcgtcc aaggccatgg gcatcatgaa ttcgtttgtg aacgacattt tcgagcgcgt  
601 cgcaggtgag gcttcccgcc tggcgcatta caacaagcgc tcgacctca cctccaggga  
661 gatccagacg gccgtgcgcc tgctgctgcc tggggagtgt gccaaagcacg ccgtgtccga  
721 gggactaag gccgtcacca agtacaccag cgctaagtaa acagtgagtt ggttgcaaac  
781 tctcaacct aacggctctt ttaagagcca cccatgttct caaagaaaga gctggtgctt  
841 gtattcctcc tctgtggcc actgacaaac ccttgtaact tgctactgtg tttttggtc  
901 tgaagtagag cagttattta actaatcctt agtgactttt ttttttga tctgccattc  
961 taatcttaga gtttaagtaag gagatgggaa attttctatt ataagttcga aaccaattaa  
1021 aatacgtag aaaccaatta aaatactcgt cggcccccg tcggttagtg atttgaaca  
1081 gtgccaagtt gcagcgggtg tcagtttgaa tttgccggg caacgccgc ccttct

**Figure 24. (Page 18 of 46)****NM 001657 Homo Sapiens amphiregulin**

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1 agacgttcgc acacctgggt gccagcggcc cagaggtccc gggacagccc gaggcgccgc
61 gcccggccgc ccgagctccc caagccttcg agagcggcgc aactcccggt tctccactcg
121 ctcttccaac acccgctcgt ttggcgga gctcgtgtcc cagagaccga gttgcccag
181 agaccgagac gccgccgtg cgaaggacca atgagagccc cgctgctacc gccggcgccg
241 gtggtgctgt cgctcttgat actcggtca gccattatg ctgctggatt ggacctcaat
301 gacacctact ctgggaagcg tgaaccattt tctggggacc acagtgtga tggattgag
361 gttacctcaa gaagtgagat gtcttcaggg agtgagattt cccctgtgag tgaatgcct
421 tctagtagtg aaccgtcctc gggagccgac tatgactact cagaagagta tgataacgaa
481 ccacaaatac ctggctatat tctgatgat tcagtcagag ttgaacaggt agttaagccc
541 ccccaaaaca agacggaaag tgaaaatact tcagataaac caaaagaaa gaaaaaggga
601 ggcaaaaatg gaaaaaatag aagaacaga aagaagaaaa atccatgtaa tgcagaattt
661 caaaatttct gattcacgg agaatgcaa tatatagagc acctggaagc agtaacatgc
721 aaatgtcagc aagaatattt cgtgaacgg tgtgggaaa agtccatgaa aactcacagc
781 atgattgaca gtattttatc aaaaattgca ttagcagcca tagctgcctt tatgtctgct
841 gtgatcctca cagctgttgc tgtattaca gtccagctta gaagacaata cgtcaggaaa
901 tatgaaggag aagctgagga acgaaagaaa ctgcacaag agaattgaaa tgtacatgct
961 atagcataac tgaagataaa attacaggat atcacattgg agtcactgcc aagtcatagc
1021 cataaatgat gagtcgggtc tcttccagt ggatcataag acaatggacc cttttgtta
1081 tgatggtttt aaactttcaa ttgtcattt ttatgctatt tctgtatata aaggtgcacg
1141 aaggtaaaaa gtatttttc aagttgtaa taatttattt aatatttaat ggaagtgtat
1201 ttattttaca gtcattaaa ctttttaac caaacagaaa aaaaaaaaaa aaaaaaaaaa
1261 aaaaaaaaaa
```



**Figure 24. (Page 19 of 46)****M90357 Human basic transcription factor 3**

1 ttatggtaa tgttctata gacatccaaa ggtcagaaac tattccatt tgaaaaatat  
 61 ctgttgtgtg ataatgtgc tgtttcttt cctcttctcc ctgacttag ggaactgtc  
 121 gcagaaagaa gaaggtggt catagaacag ccacagcaga tgacaaaaaa cttcagttct  
 181 ccttaaagaa gtaggggta aacaatatct ctggtattga agaggcaagt atcaaattt  
 241 gtacttttaa aaaacaagat ttggctggga aaagttaacg ttaatgcatt aaatgggtg  
 301 ttgggtttt ttaacttag ggactcaaa gtccctaaga tgtgttcta ccataaatta  
 361 ataaatatca gggagctcat taagtctgaa tgctattaga atacatattc cattccaggc  
 421 aaaattcac ctgtgcttac acgtgaaata ctagttagcc agagctagt taataaaca  
 481 ttgttttta aagagactgg tcagcattgc taattaaat tttcttttc ttaatagggtg  
 541 aatatgttta caaaccaagg aacagtgtc cactttaaca accctaaagt tcaggcatct  
 601 ctggcagcga acactttcac cattacaggc catgctgaga caaagcagct gacagaaatg  
 661 ctaccagca tctaaacca gcttgggtgc gatagtctga ctagttaag gagactggcc  
 721 gaagctctgc ccaacaatg tgagtctct agtaatggtt ttaccaggga attactcatt  
 781 tagcagctga ttctgatct cagggtcag aatggatatg agtatttta agtttgaaa  
 841 tgcaagcttt aaaaataaca gatttgaac tgatttaag caactgtcct tgctcaagtt  
 901 tgcagtaatt gatgtagcgt gccatgattg ttacacttga tttgtggaa tgtttctac  
 961 ttacttgatt tggatcagat actttatta actagaaatg atgaaatgt taattgggtg  
 1021 ctttgccaat aactactgt aagtttgaa ttgaaaaaa aattagtga aattatgaaa  
 1081 ttacttcagt tcatctata tagttcgtat taccagtaat ctttaaaaa tggcttgcca  
 1141 gtattctggc atttaatta cagtgtgata gggatttatt cggggcagaa aatagttag  
 1201 ctgaatafac atctgaggat ttggcagtg tatgctgtt tctgtgcta aaatttgaa  
 1261 gaataggaat gcaggaggaa gtcagaggct tatatatggc tcttagtta ccatgtttt  
 1321 tctaggtatt gacttaact gcctcaatt tcattttat tatcacttg agttgcaggt  
 1381 tctaaactgt cagggtcttc agagctgaaa taggctttg aagtatccca ctgatgcctg  
 1441 tatgggcta gtacataact ctctgtgta cgttcattt cttgtgtgat aaaggagagt  
 1501 ggatgcttac cactcacaga ctcttaatt ttttacttt aactttttc atttcagtaa  
 1561 gtggtgtgtg agcatcacc ttatgccaca cacagagtag ttgagaaat ggcatttca  
 1621 ttgtctccc aaaatctcac catgatttg tatgtgggt ttacctgcac tctaaagatt  
 1681 ccctactgcc cttatactac ctgagccta tgggtggcag aggattgaaa gattggtatg  
 1741 gaattgttt gttggcgttc ctagtattt aacctttg tagacattag aatatcatgt  
 1801 tattgatagt atcataggat aaaatccca atgtcccta tcatggaat aagtgtaac  
 1861 aacacttgc attcatctg ttctttttt tttttttt ttttttgg tgaatttta  
 1921 ttaaaaacct agacaaataa tgtttacatt ttctttcat agctgtggat ggaaaagcac  
 1981 cactgtctac tggagaggat gatgatgat aagttccagg taggaacgtt tgcctgtgtg  
 2041 taacctagag aatcttagcc aaggagaaat aagaaatct ttaggaaaa actaccagg  
 2101 gaagaggggt gtaagttaa gatggacata gatcttact agaagagaa aaataatgca  
 2161 gtattagga attgagaatt atgtttatag acttgacttg gctgtttct gtttgggatc  
 2221 ccaaggatgt gtaggtatct aacctaaat attgaataaa taagtatata tatatgtac  
 2281 cctaaatata actattacct gcagagcact aatgacctt gctccctact ttgaaactca  
 2341 tgaatttaca agaaggtgtg gattgttca ggtatcttg gatatatata tgcattctaa  
 2401 aatcttagc agcataactc ctttgggaa tcagaggatt ttgtctcta cctgttattg  
 2461 gataaattta cgttcttcta aaatattat tgggcaggag aatcactgga ctcataaata  
 2521 ttccacttt gcatagacag gtatccctag gaatcaggaa aatttaaca ttgtgtgta  
 2581 ttgtattct tggttctgt cccctactat tgaccaatgt agagatggga agaggggggc  
 2641 attttttct cttttttt ttttgcatt ctgttctg ggcctatgac acagtattta  
 2701 tcatcattgg caaatgaatg ctcttctt catccctt taatatctga taattttt  
 2761 tagattggt ttttaagaa ttctactct tttctttc ctgatcttg tggagaattt

**Figure 24. (Page 20 of 46)**

2821 tgatgaggct tccaagaatg aggcaaactg aattgagtca acttctgaag ataaaacctg  
2881 aagaagtta ctgggagctg ctattttata ttatgactgc ttttaagaa aattttgtt  
2941 tatggatctg ataaaatcta gatctcta attttaagc ccaagcccct tggacactgc  
3001 agctcttttc agttttgct tatacacaat tcattcttg cagctaatta agccgaagaa  
3061 gcctgggaat caagtttgaa acaaagatta ataaagttct ttgcctagt atacagttt  
3121 attttttat ttattgacac cgatctgtac acagtaaaaa aaattgctta tagaaagcta  
3181 atcatggcat gtaatatggc tgataacctt tggaatttga ttaaagattt aaaatcacgg  
3241 tgtaagtgt acaaagggtg tataaagttc tcaggtttga aaactttgtc tccaacagtc  
3301 cttagtctt ccatgattta tatggtgggt gtaaatatga gaatagagta ttcttagtg  
3361 gataaacaga catttctccc tgatattctc tattgtaagc atatgttaag tgcctttat  
3421 gaattaccct cgggtgtatc ttctttatt cctcaatttg tgaagaacta atagctccat  
3481 ttgtagatg taacctgagg tttagaactt ctaaaaagta aaagtaatct ccagatccct  
3541 tcttgtagg atattttata aggtgacttg gaaaaggtag tgtttagaat aggagtggct  
3601 cctgggtcat tgtctttcc ttaagtgtaa cacctaata atgaataggg ttatgtttt  
3661 atttaataaa aaatatacag taaaattgag catatacagt taaaagaatt tataatgtct  
3721 gccactataa ccaggcttac cagacagttt catggtccag aaaatcccta aacatagggt  
3781 tacttttaa cattttacaa attacaatga aacaattgtg taatctgaac caaggccatt  
3841 tgaggagaaa tagttctact tgatgggtat ttatttttaa attttcata gcaatttgca  
3901 agtacctttt gaaagtatta tcagttgtat ctaaatgca ctattaaccg tgg

**Figure 24. (Page 21 of 46)****NM 006219 Homo sapiens phosphoinositide-3-kinase, p110 subunit**

1 atgtgcttca gtttcataat gcctcctgct atggcagaca tccttgacat ctgggcggtg  
 61 gattcacaga tagcatctga tggctccata cctgtggatt tcctttgcc cactgggatt  
 121 tatatccagt tggaggtacc tcgggaagct accatttctt atattaagca gatgttatgg  
 181 aagcaagttc acaattaccc aatgttcaac ctcttatgg atattgactc ctatatgtt  
 241 gcatgtgtga atcagactgc tgtatatgag gagcttgaag atgaaacacg aagactctgt  
 301 gatgtcagac ctttcttcc agttctcaa ttagtgacaa gaagttgtga ccaggggaa  
 361 aaattagact caaaaattgg agtccttata ggaaaaggtc tgcattgaatt tgattcctg  
 421 aaggatcctg aagtaaatga atttgaaga aaaatgcgca aattcagcga ggaaaaaatc  
 481 ctgtcacttg tgggattgtc ttgatggac tggctaaaac aaacatatcc accagagcat  
 541 gaaccatcca tccctgaaaa cttagaagat aaactttatg ggggaaagct catcgtagct  
 601 gttcattttg aaaactgccg ggacgtgtt agcttcaag tgtctcctaa tatgaatcct  
 661 atcaaagtaa atgaattggc aatccaaaaa cgtttgacta ttcattgggaa ggaagatgaa  
 721 gttagccct atgattatgt gttgcaagtc agcgggagag tagaatatgt tttgtgtat  
 781 catccactaa ttcagttcca gtatatccgg aactgtgtga tgaacagagc cctgccccat  
 841 ttatacttg tggaatgtcg caagatcaag aaaatgtatg aacaagaaat gattgccata  
 901 gaggtgccca taaatcgaat tcatctaat ctctcttc cattaccacc aaagaaaaca  
 961 cgaattatt ctcatgttg ggaaataac aacccttcc aaattgtctt ggttaaggga  
 1021 aataaactta acacagagga aactgtaaaa gttcatgtca gggctggtct tttcatggt  
 1081 actgagctcc tgtgtaaaac catcgtaacg tcagaggat cagggaaaaa tgatcatatt  
 1141 tggaatgaac cactggaatt tgatattaat atttgact taccaagaat ggctcgatta  
 1201 tgtttgctg tttatgcagt ttggataaa gtaaaacga agaaatcaac gaaaactatt  
 1261 aatccctcta aatatcagac catcaggaaa gctggaaaag tgcattatcc ttagcgtgg  
 1321 gtaaatcga tggttttga ctttaaagga caattgagaa ctggagacat aatattacac  
 1381 agctggtctt catttctga tgaactgaa gaaatgtga atccaatggg aactgtcaa  
 1441 acaaatccat atactgaaaa tgcaacagct ttgcatgta aatttccaga gaataaaaaa  
 1501 caaccttatt attacctcc ctgcgataag attattgaa aggcagctga gattgcaagc  
 1561 agtgatagtg ctaattgtgc aagtcgaggt ggaaaaaagt ttctcctgt attgaaagaa  
 1621 atcttggaac gggatccctt gtctcaactg tgtgaaatg aaatggatct tatttgact  
 1681 ttgcgacaag actgccgaga gattttcca caatcactgc caaaattact gctgtcaatc  
 1741 aagtggataa aacttgagga tgtgtctcag ctccaggcgc tcttcagat ttggcctaaa  
 1801 ctgccccccc gggaggccct agagcttctg gatttcaact atccagacca gtacgttga  
 1861 gaatatgctg taggtgcct gcgacagatg agtgaatgaa aactttctca atatcttta  
 1921 caactggtgc aagtgttaaa atatgagcct ttcttgatt gtgccctctc tagattccta  
 1981 ttgaaaagag cacttggtaa tcggaggata gggcagtttc tattttggca tcttaggtca  
 2041 gaagtgcaca ttctgctgt ctactgacaa ttggtgtca tcctgaagc atactgccg  
 2101 ggaagtgtgg ggcacatgaa agtgccttct aagcaggttg aagcactcaa taagttaaaa  
 2161 actttaataa gtttaataa actgaatgcc gtgaagttaa acagagccaa agggaaggag  
 2221 gccatgcata cctgtttaa acagagtgtc taccgggaag cctctctga cctgcagtca  
 2281 cccctgaacc catgtgttat ccttcagaa ctctatgttg aaaagtcaa atacatggat  
 2341 tccaaaatga agccttttg gctgtgtatc aataacaagg tatttggtga ggattcagtt  
 2401 ggagtgattt ttaaaaatgg tgatgattt cgacaggata tgttgacact ccaaatgttg  
 2461 cgcttgatgg atttactctg gaaagaagct ggttggatc ttggatgtt gccttatggc  
 2521 tgtttagcaa caggagatcg ctctggcctc attgaagtgt tgagcacctc tgaacaatt  
 2581 gctgacattc agctgaacag tagcaatgtg gctgtcgcag cagccttcaa caaagatgcc  
 2641 ctctgaact ggcttaaga atacaactct ggggatgacc tggaccgagc cattgaggaa  
 2701 ttacactgt cctgtgctg ctactgtga gcttctatg tcctgggat tggtagacaga

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2761 catagtgaca acatcatggt caaaaaaact ggccagctct tccacattga ctttgacat  
2821 attcttgaa attcaaate taagtttggc attaaaagg agcgagtgcc tttattctt  
2881 acctatgatt tcatccatgt cattcaaca ggaaaaacag gaaatacaga aaagtttggc  
2941 cggttccgcc agtgttgtga ggatgcatat ctgattttac gacggcatgg gaatctctc  
3001 atcactctct ttgcgctgat gttgactgca gggcttctg aactcacatc agtcaaagat  
3061 atacagtatc ttaaggactc tctgcatta gggaagagtg aagaagaagc actcaaacag  
3121 ttaagcaaa aatttgatga ggcgctcagg gaaagctgga ctactaaagt gaactggatg  
3181 gccacacag ttcgaaaga ctacagatct taa

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**X04412      Human Gelsolin**

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1 gccgtgtcgc caccatggct ccgcaccgcc ccgcgcccgc gctgctttgc gcgctgtccc
61 tggcgctgtg cgcgctgtcg ctgcccgtcc gcgcggccac tgcgtcgcgg ggggcgtccc
121 aggcgggggc gcccagggg cggtgtccc aggcgcggcc caacagcatg gtggtggaac
181 accccgagtt cctcaaggca gggaaggagc ctggcctgca gatctggcgt gtggagaagt
241 tcgatctggt gcccggtccc accaaccttt atggagactt cttcacgggc gacgcctacg
301 tcactctgaa gacagtgcag ctgaggaacg gaaatctgca gtatgacctc cactactggc
361 tgggcaatga gtgcagccag gatgagagcg gggcgccgc catctttacc gtgcagtgg
421 atgactacct gaacggcccg gccgtgcagc accgtgaggt ccagggttc gagtcggcca
481 ctttctagg ctactcaag tctggcctga agtacaagaa aggaggtgtg gcatcaggat
541 tcaagcacgt ggtaccaac gaggtggtgg tgcaagact cttccaggtc aaaggcgccg
601 gtgtgtccg tgccaccgag gtacctgtgt cctgggagag ctcaacaat ggcgactgct
661 tcactctgga cttgggcaac aacatccacc agtgggtgtg ttccaacagc aatcggtatg
721 aaagactgaa ggccacacag gtgtccaagg gcatccggga caacgagcgg agtgccggg
781 cccgagtgca cgtgtctgag gagggcactg agcccgaggc gatgtccag gtgctgggccc
841 ccaagccggc tctgcctgca ggtaccgagg acaccgcaa ggaggatgcg gccaacgca
901 agctggccaa gctctacaag gtctccaatg gtgcagggac catgtccgc tccctctgg
961 ctgatgagaa ccccttcgcc cagggggccc tgaagtcaga ggactgcttc atcctggacc
1021 acggcaaaaga tgggaaaate ttgtctgga aaggcaagca ggcaaacacg gaggagagga
1081 aggtgtccct caaacagcc tctgacttca tcaccaagat ggactacccc aagcagactc
1141 aggtctcggc ctttctgag ggcggtgaga cccactgtt caagcagttc ttcaagaact
1201 ggcgggaccc agaccagaca gatggcctgg gcttgccta ctttccagc catatcgcca
1261 acgtggagcg ggtgcccttc gacgccgcca ccctgcacac ctccactgcc atggccgccc
1321 agcacggcat ggatgacgat ggcacaggcc agaaacagat ctggagaatc gaaggttcca
1381 acaaggtgcc cgtggaccct gccacatatg gacagttcta tggaggcgac agctacatca
1441 ttctgtacaa ctaccgccat ggtggccgcc aggggcagat aatctataac tggcagggtg
1501 cccagtctac ccaggatgag gtcgtgcat ctgccatct gactgctcag ctggatgagg
1561 agctgggagg taccctgtc cagagccgtg tggccaagg caaggagccc gccaccta
1621 tgagcctgtt tgggtgggaag cccatgatca tctacaagg cggcacctcc cgcgaggcg
1681 ggcagacagc cctgccagc acccgctct tccaggtccg cgccaacagc gctggagcca
1741 cccgggctgt tgaggtattg cctaaggctg gtgactgaa ctccaacgat gcctttgtc
1801 tgaaaacccc ctacccgcc tacctgtggg tgggtacagg agccagcgag gcagagaaga
1861 cgggggcccc gagctgtctc aggtgtctgc gggcccaacc tgtgcagggt gcagaaggca
1921 gcgagccaga tggcttctgg gaggccctgg gcgggaaggc tgcctaccgc acatccccc
1981 ggctgaagga caagaagatg gatgccatc ctctcgctt ctttgcctgc tccaacaaga
2041 ttggacgttt tgtatcgaa gaggttctg gtgagtcac gcaggaagac ctggcaacgg
2101 atgacgtcat gcttctggac acctgggacc aggtcttgt ctgggttga aaggattctc
2161 aagaagaaga aaagacagaa gccttgactt ctgctaagcg gtacatcgag acggaccag
2221 ccaatcgga tggcgagcg ccatcaccg tggtaagca aggtttgag cctccctct
2281 ttgtgggctg gttccttggc tgggatgatg attactggtc tgtggacccc ttggacaggg
2341 ccatggctga gctggctgcc tgaggagggg caggggccac ccatgtcacc ggtcagtgcc
2401 ttttgaact gtccttccct caaagaggcc ttagagcgag cagagcagct ctgctatgag
2461 tgtgtgtgtg tgtgtgtgt gttttttt ttttttta cagtatcaa aaatagccct
2521 gcaaaaattc agatccttg caaaattgtc taaaatgtca gtgtttgga aattaaatcc
2581 aataaaaaca tttgaagtg tg

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**NM 001759 Homo sapiens Cyclin D2**

1 agagcgagca ggggagagcg agaccagttt taaggggagg accggtgcga gtgaggcagc  
 61 cccgaggctc tgctcgccca ccaccaatc ctgcctccc ttctgtcca cttctctct  
 121 ctgccctcac ctctcccccg aaaacccctc atttagccaa aggaaggagg tcaggggaac  
 181 gtctcccct cccttccaa aaaacaaaa cagaaaaacc ctttccagg cgggggaaag  
 241 caggagggag agggggcggc gggctggcca tggagtgct gtgccacgag gtggaccgg  
 301 tccgcagggc cgtgcgggac cgcaacctgc tccgagacga ccgcgtctg cagaacctgc  
 361 tcaccatcga ggagcgtac ctccgcagt gctctactt caagtgcgtg cagaaggaca  
 421 tccaacctca catgcgcaga atggtggcca cctggatgct ggaggtctgt gaggaacaga  
 481 agtgcaaga agaggtcttc cctctggcca tgaattacct ggaccgttc ttgctgggg  
 541 tcccactcc gaagtcccat ctgcaactcc tgggtgctgt ctgcatgtc ctggcctcca  
 601 aactcaaaga gaccagcccg ctgaccgcg agaagctgtg cattacacc gacaactcca  
 661 tcaagctca ggagctgtg gagggggaac tgggtggtg ggggaagtg aagtgggaac  
 721 tggcagctgt cactctcat gactcattg agcacatct gcgcaagctg cccagcagc  
 781 gggagaagct gtctctgat cgcaagcatg ctacagacct cattgctctg tgtgccaccg  
 841 accttaagt tgcatgtac ccaccgtca tgcgcgaac tggaaagtgt ggagcagcca  
 901 tctgtgggt ccagcaggat gaggaagtga gctcgtcac ttgtgatgc ctgactgagc  
 961 tgctggctaa gatcaccaac acagacgtg attgtctcaa agcttgccag gagcagattg  
 1021 aggcgggtgct cctcaatagc ctgcagcagt accgtcagga ccaacgtgac ggateccaagt  
 1081 cggaggatga actggacca gccagcacc ctacagacgt gcgggatgc gacctgtgag  
 1141 gatgccagtt gggccgaaag agagagacgc gtccataatc tggctcttc ttttttgg  
 1201 ttgttttgt tctttgtgt itagggtgaa acttaaaaaa aaattctgc cccacctag  
 1261 atcatatta aagatctttt agaagtga gaaaaaggc ctacgaaac ggaataataa  
 1321 aaagcatttg gtgcctatt gaagtacagc ataagggaat ccttgtata tgcgaacagt  
 1381 tattgttga ttatgtaaaa gtaatagtaa aatgcttaca ggaacacctg cagagtagtt  
 1441 agagaatatg tatgctgca atatgggaac aaattagagg agacttttt tttcatgtt  
 1501 atgagctagc acatacccc cttgtagta taattcaag gaactgtgta cgccattat  
 1561 ggcattgatta gattgcaaag caatgaactc aagaaggaa tgaaataagg agggacatga  
 1621 tggggaagga gtacaaaaca atctcaac atgattgaac cattgggat ggagaagcac  
 1681 ctttgcctc agccacctg tactaagta ggagtgtagt tggatctcta catatgtc  
 1741 ctctgtctg ctacagtagc tctaccta aaaaagatgt tttatttgc cagtggaca  
 1801 caggtgattg gctcctgggt tcatgttct gtgacatct gcttctctt ccaaatgcag  
 1861 ttcattgcag acaccacct attgctatc aatggggaaa ttagctatg ggccataacc  
 1921 aaaactcaca tgaacggag gcagatggag accaagggtg ggateccaga tggagtctt  
 1981 tctgtattg tatttaaaag ggtaattgg cttggcatt tctcttga aaaaaacta  
 2041 ttttgggtgc tgattggcat gtctggtca cagtttagca ttgtataaa ccattccatt  
 2101 cgaaaagcac ttgaaaaat tgtcccgag cgatagatgg gatggttat gcaagtcag  
 2161 ctgaatactc ctccctctt ctctttgcc cctccctc ctgccccag tctgggtac  
 2221 tcttgcctc tggatctgg cgttcttgg tacacagtc tgggttct accaggactc  
 2281 aagagacacc cctctctgt gacattcca tcacaacatt cctcagaca gcctgtaaac  
 2341 taaaatctgt taccattctg atggcacaga aggatcttaa ttccatctc tatactctc  
 2401 ctttggacat ggaaagaaaa gttattgctg gtgcaaatg agatggctga acatcagggt  
 2461 gtggcattt gtccctttt cgtttttt ttttttatt gttgtgta atttattgc  
 2521 aaagttgat tcagcgact tgaattttc ttctctcca ctcttagag gcattcagtt  
 2581 agcaaagggt ttggagcaac aactttttt tttttttg cacaattgta attgacaggt  
 2641 aatgaagcta tttgtaaaa tattgcctt ttaagtaaa aaagaaaaat cagaacaggg  
 2701 ctatttgaag aattatttta tacacagatt ctgcctgtt tcatagtat aggggtgaag  
 2761 acggaaaaa atctaagggt ctctcattt ttaattttg tttgttcag tttgtttt

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2821 tttttttt gcgctgctaa gaagctaaag tcacccatcc ttattcacgt tgacagtacc  
2881 tagctgtaat gtttcacaga gtgtgctgct atttataaa cattttata atatattatt  
2941 ttactgttta aattccaagt cctgaagtag atgggtgaga tatgagttct tcgtactgga  
3001 aaagcccttc cgtagtttgt ttctcttg tagcatatc atgggtgttt ttttttct  
3061 ttttgggtt ttgggtttt ttttttct ctgatcacat tctcaaaga cggagtattc  
3121 ttacctcag gtttactgga caaaatcaat aactacaaaa ggcaatgatt cacgctttg  
3181 tttcataat acctacaaac cgtacagtt ctgcttgga gccattcgc atgaggaata  
3241 cagaagcagt gtgagcagg ctagctccct ctgagtgga aggcaggcgc gtctcactcc  
3301 caggacctt ttggctcatg gaggccatcg ggctccagt tagaccctgg tatcctcatc  
3361 atgatggaaa aaatacattg aaccaaggga tctcctcc cttcaaggc agacgttcag  
3421 tacaacatt tatcggttag gtcagatgt cgtaatgtc acttaggtac caggtgtcag  
3481 gaaacagact aaaaagaatt ccaccaggct gtttgagat cctcatctg gagcttttc  
3541 aaaagcggg cttcatctgc aaaggccct tcatctga agttttccc ctccgtctt  
3601 cccctccct ggcatggaca cttgtgtt aggatcatct ctgcaggtt ctaggtctg  
3661 aatctgcgag tagatgaacc tgcagcaagc agcgtttatg gtgcttcct ctccctcctc  
3721 tgtctcaaac tgcgcaggca agcactatgc aagcccaggc cctctgctga gcggtactaa  
3781 acggtcgggt ttcaatcac actgaattgg caggataaga aaaataggtc agataagtat  
3841 gggatgatag tgaaggag gtgaaggagc tgcctctca cagagtgaa attccagatg  
3901 agtcagtctc ttgggaagtg tgttagaag ggttcaggac ttgtgagtt agcatgacc  
3961 taaaattcta ggggattct ggtgggaca tgggtggga atttgaagt ttggagagg  
4021 gaagtggagc agccagcaag taagtagcc agagtttct caagagccag cttgtcag  
4081 cacactctcc tgggcccacaa ggagtcac ggaatggga aagtgggaac cttggagtc  
4141 ttgggaatct tggagcctaa agagaaccg aggtgcaaat tcattcatg gtgactgacc  
4201 cttgagctta aacagaagca gcaaatgaaa gaaccggaca aataaggaag ggcacaagcc  
4261 taccgactc tattacagt ctgtaactt ccactctcc ttagtccc aggccctgg  
4321 gtcttctag cttttctt tccatcctt ggggcctgt gtgatgatg gtgtgggct  
4381 gccgatgga aagtcgggg ttgttagct ttctgctg ctctgctta aacacaagaa  
4441 ggaatcctg attttgct ctcttagct cttagctct ttgtaggag tttgtcca  
4501 gaggagctc ccccttga tttgaactg ctctttgt tgtgtgtt cttctctc  
4561 ttttctac ctccactaa aggggtcca aattactc gtctttct acctgtgt  
4621 gtttctat ctctttact tcatctgt ttttttcc tcatcagt ggggccgagt  
4681 tgtccccc gctgcccc tttgatct tccctctt tggccaaac ctaggggga  
4741 gaaatcctag tatccaaaa atatagcta agcataatta aactccatgc ggtccataa  
4801 cagccaagaa gcctgcagga gaaagccaag ggcagttcc tccgcagaac acccatcg  
4861 tgctgagagg cgagctcct gaagaaggg ctgtctcc aggagcctt atttgaact  
4921 gcctcaggac cccactggag agcacagcat gccttactac tgggtcatc ttgtctatg  
4981 tgctctgac tggaggtct gttctgctc ttatagcca ggtcaggggc acacatggct  
5041 taagtgacaa agccagagga gaagacaacc ctgacagcat cacgtgcat ccattgcta  
5101 gcaggattgg caactctca gacggagctg cgttccctg cagtctagca ccttagggc  
5161 ctctccagac tgtccctgg gagctctgg actgaaagt taagaacata aggcaggatc  
5221 agatgactct ctcaaagg gcagggggaat ttctctcca tgggccacag gggacagggc  
5281 tgggagaaga aatagactg caccatgt catgtaaata attgatttc tagtcaaga  
5341 agataatatt ggtagtgtg gaattggagg taggaaggg aggaagtct agtaagccag  
5401 ttggttcta agccaaaagg attcctctt gttatctct gagacagtc aacctgaga  
5461 atagcttaa aggggaaatt aatgctgaga tgataaagc ccttaagcc aacaaacct  
5521 ctgtagctat agaattagtg caggttcta ttggttgga ctgagagca ttacaagag  
5581 ctgttcatgc agccatccat ttgtcaaaa taggtaaga agattcaaga ggtatttat  
5641 tacttctca taccatgg cttttgatg ttctggatc taaacaacc agaattgtca  
5701 ttacggcac aacgatacta cattctgtg tgtctgtt taaactggc tgggtatca

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5761 gaccctattc tcggctcagg tttgagaag ccatcagcaa atgtgtacgt gcatgctgta  
5821 gctgcagcct gcatcccttc gcctgcagcc tactttgggg aaataaagtg cttactgac  
5881 thtagccatt acagtatcca atgtctttg acaggtgcct gtccttgaaa aacaaagttt  
5941 ctatttttat ttttaattgg tttagtctt aactgctggc caactcttac atcccagca  
6001 aatcatcggg ccattggatt tttccatta tttcatcac cttatatca tgtacctag  
6061 atctctctct ctctctctct tctcagttat atagtttctt gtcttggaact ttttttct  
6121 tttcttttc tttttttt tgctttaaaa caagtgtgat gccatatcaa gtccatgta  
6181 ttcttcaca gtgtactcta taagaggtgt ggggtgtctgt ttggtcagga tgtagaaag  
6241 tgctgataag tagcatgac agtgtatgcg aaaagggttt taggaagtat ggcaaaaatg  
6301 ttgtattggc tatgatggtg acatgatata gtcagctgcc ttttaagagg tcttatctgt  
6361 tcagtgttaa gtgattfaaa aaaataataa cctgttttct gactagtta aagatggatt  
6421 tgaanaatggt ttgaatgca attagggtat gctatttga caataaactc acctgacct



**Figure 24. (Page 27 of 46)****NM 004444 Ephrin Receptor (EphB4)**

1 cgtccacccg cccagggaga gtcagacctg ggggggag gagcccccaa actcagttcg  
 61 gatctaccc gagtgaggcg gcgcatgga gtcgagggtg ctgctctgct gggcttcgtt  
 121 ggccgcagct ttgaagaga cctgctgaa cacaaaattg gaaactgctg atctgaagtg  
 181 ggtgacattc ctcaggttg acgggcagtg ggaggaactg agcggcctgg atgaggaaca  
 241 gcacagcgtg cgcacctacg aagtgtgtga agtgcagcgt gccccgggccc agggccactg  
 301 gcttcgcaca ggttggttcc cagggcgggg cgccgtccac gtgtacgcca cgtgcgctt  
 361 caccatgctc gaggcctgt cctgcctcg ggctgggagc tctgcaagg agaccttcac  
 421 cgtctctac tatgagagcg atgcggacac ggccacggcc ctcacgccag cctggatgga  
 481 gaaccctac atcaaggttg acacggtggc cgcggagcat ctcacccgga agcgcctgg  
 541 ggccgaggcc accgggaagg tgaatgtcaa gacgtgctg ctgggaccgc tcagcaaggc  
 601 tggtctctac ctggccttc aggaccaggg tgcctgcatg gccctgctat cctgcacct  
 661 ctctacaaa aagtgcgccc agctgactgt gaacctgact cgattcccgg agactgtgcc  
 721 tcgggagctg gttgtgcccg tggccggtag ctgctgggtg gatgccgtcc ccgccctgg  
 781 cccagcccc agcctctact gccgtgagga tggccagtgg gccgaacagc cggtcacggg  
 841 ctgcagctgt gtcgggggt tcgaggcagc tagggggaac accaagtgc gagcctgtgc  
 901 ccagggcacc tcaagcccc tgcaggaga agggctctgc cagccatgcc cagccaatag  
 961 cactctaac accattggtat cagccgtctg ccagtgcgc gtcgggtact tccgggcacg  
 1021 cacagacccc cggggtgcac cctgcaccac cctccttcg gctccgcgga gcgtggttc  
 1081 ccgctgaac ggctcctccc tgcacctgga atggagtgc ccctggagt ctggtggccg  
 1141 agaggacctc acctacgccc tccgtgcgc ggagtgcga cccggaggct cctgtgcgc  
 1201 ctgcggggga gacctgactt ttgaccccg ccccgaggac ctggtggagc cctgggtgtg  
 1261 ggttcgaggg ctactgcgg acttcaccta taccttgag gtcactgcat tgaacgggt  
 1321 atctcctta gccacggggc cgtccatt tgagcctgtc aatgtacca ctgaccgaga  
 1381 ggtacctcct gcagtgtctg acatccgggt gacgcggtcc tcaccagca gcttgacct  
 1441 ggctgggct gttccccgg caccagtgg gccgtggctg gactacgagg taaaatacca  
 1501 tgagaagggc gccgagggtc ccagcagcgt gcggttctg aagacgtcag aaaaccgggc  
 1561 agagctgcgg gggctgaagc ggggagccag ctacctggtg caggtaggg cgcgtctga  
 1621 ggccggctac gggcccttc gccaggaaca tcacagccag accaactgg atgagagcga  
 1681 gggctggcgg gacagctgg cctgattgc gggcacggca gtcgtgggtg tggctctgt  
 1741 cctggtgtg attgtgtc cagtctctg ctcaggaag cagagcaatg ggagagaagc  
 1801 agaattatcg gacaaacag gacagtatc catcgacat ggtactaagg tctacatga  
 1861 ccccttcat tatgaagacc ctaatgagc tgtgaggga tttgaaaag agatcgatg  
 1921 ctctacgtc aagattgaag aggtgattgg tgcaggtgag tttggcagg tgtccgggg  
 1981 gcggctcaag gccccaggga agaaggagag ctgtgtggca atcaagacc tgaagggtg  
 2041 ctacacggag cggcagcggc gtgagttct gagcaggcc tccatcatg gccagttga  
 2101 gcacccaat atcatccgc tggaggcgt ggtaccaac agcatcccc tcatgattt  
 2161 cacagagttc atggagaac gcgcctgga ctcttctc cggctaaac acggacagt  
 2221 cacagtcac cagctcgtg gcagctgcg ggcatcgcc tcgggcatgc ggtacctgc  
 2281 cgagatgagc tacgtccac gagacctggc tgctcgcaac atcctagtca acagcaacct  
 2341 cgtctgcaaa gtgtctgact ttggccttc cgattctc gaggagaact ctccgatcc  
 2401 cacctacag agtccctgg gaggaaagat tccatccga tggactgcc cggaggccat  
 2461 tgcctccgg aagttcact ccgccagtga tgcctggagt tacgggattg tgatgtgga  
 2521 ggtgatgtca tttggggaga ggccgtact ggacatgag aatcaggacg tgatcaatgc  
 2581 cattgaacag gactaccggc tgccccgcc ccagactgt ccacctccc tccaccagc  
 2641 catgctggac tgttggcaga aagaccgga tggccggccc cgttcccc aggtgtcag  
 2701 cgccctggac aagatgatcc ggaacccgc cagctcaaa atcgtggccc gggagaatg  
 2761 cggggcctca caccctctc tggaccagc gcagctcac tactcagctt ttgctctgt

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2821 gggcgagtgg cttcggggcca tcaaaatggg aagatacgaa gaaagtctcg cagccgctgg  
2881 ctttggctcc ttcgagctgg tcagccagat ctctgctgag gacctgctcc gaatcggagt  
2941 cactctggcg ggacaccaga agaaaatctt ggccagtgtc cagcacatga agtcccaggc  
3001 caagccggga accccgggtg ggacaggagg accggccccg cagtactgac ctgcaggaac  
3061 tccccacccc agggacaccg cctccccatt ttccggggca gagtggggac tcacagagge  
3121 cccagccct gtgccccgt ggattgcaact ttgagcccg ggggtgagga gttggcaatt  
3181 tggagagaca ggatttggg gttctgcat aataggagg gaaaatcacc cccagccac  
3241 ctgggggaac tcagaccaa gggtgagggc gccttccct caggactggg tgtgaccaga  
3301 ggaaaaggaa gtgccaaca tctccagcc tcccagggtg ccccccac ctgatgggt  
3361 gcgtcccg agacaaaga gagtgtgact ccctgccag ctccagagt ggggggctgt  
3421 ccagggggc aagaagggt gtcagggcc agtgacaaa tcattgggt tttagtccc  
3481 aactgtgc tgcaccacc aaactcaatc atttttcc ctgtaaatg cccctcccc  
3541 agctgctgcc ttcatattga aggttttga gttttgtt tggcttaat ttttcccc  
3601 gtcccttt ttttcttcg tttgtttt ctaccgtcct tgcataact ttgtgtgga  
3661 gggaacctgt ttactatgg cctccttgc ccaagtga acagggggcc atcatcatgt  
3721 ctgtttccg aacagtgcct tggcatccc acatccccg accccgcctg ggaccccaa  
3781 gctgtgtcct atgaagggt gtgggtgag gtagtga aaa ggcggtagt tgggtgtgga  
3841 acccagaaac ggacccggt gcttgagggt gttctaat tatattaaa aaagtaact  
3901 ttgtataaa taaaagaaaa tgggacgtgt ccagctcca ggggt

**Figure 24. (Page 29 of 46)****M18737 Human Hanukah Factor /granzyme A**

1 atgaggaact cctatagatt tctggcatcc tctctctcag ttgtcgttcc tctctcgta  
61 attcctgaag atgtctgtga aaaaattatt ggaggaaatg aagtaactcc tcattcaaga  
121 ccctacatgg tctacttag tcttgacaga aaaaccatct gtgctggggc ttgattgca  
181 aaagactggg tgttgactgc agctcactgt aactgaaca aaaggccca ggtcattctt  
241 ggggctcact caataaccag ggaagagcca acaaacaga taatgcttgt taagaaagag  
301 ttccctatc catgctatga ccagccaca cgcgaagggtg acctaaact ttacagctg  
361 acggaaaaag caaaaattaa caaatatgtg actatccttc atctacctaa aaagggggat  
421 gatgtgaaac caggaacat gtgccaagtt gcagggtggg ggaggactca caatagtga  
481 tcttggtccg atactctgag agaagtcaat atcaccatca tagacagaaa agtctgcaat  
541 gatcgaaatc actataattt taaccctgtg attggaatga atatggttg tgctggaagc  
601 ctccgagggtg gaagagactc gtgcaatgga gattctggaa gccctttgtt gtgcgagggt  
661 gttttccgag gggtcacttc ctttggcctt gaaaataaat gcggagacc tcgtgggcct  
721 ggtgtctata ttctctctc aaagaaacac ctcaactgga taattatgac tatcaaggga  
781 gcagttaaa taaccgttc ctttcattta ctgtggcttc ttaatcttt caca

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**NM 000551 von Hippel-Lindau tumor suppressor (VHL)**

1 acgcagctcc gccccgcgtc cgacccgcgg atcccgcggc gtccggcccc ggtggtctgg  
 61 atcgcggagg gaatccccc gagggcggag aactgggacg aggccgaggt aggcgcggag  
 121 gaggcaggcg tcgaagagta cggccctgaa gaagacggcg gggaggagtc gggcggcag  
 181 gagtccggcc cggaagagtc cggcccgagg gaactgggcg ccgaggagga gatggaggcc  
 241 gggcggccgc ggcccgtct gcgtcgggtg aactcgcgcg agccctccca ggtcatcttc  
 301 tgcaatcgca gtccgcgcgt cgtgctgccc gtatggctca acttcgacgg cgagccgcag  
 361 ccctacccaa cgtgcccgc tggcacgggc cgcgcacatc acagctaccg aggtcacctt  
 421 tggctcttca gagatgcagg gacacacgat gggcttctgg ttaacaaac tgaattattt  
 481 gtgcatctc tcaatgttga cggacagcct attttgcca atatcacact gccagtgtat  
 541 actctgaaag agcgatgcct ccaggttgct cggagcctag tcaagcctga gaattacagg  
 601 agactggaca tcgtcaggtc gctctacgaa gatctggaag accacccaaa tgtgcagaaa  
 661 gacctggagc ggctgacaca ggagcgcat gacatcaac ggatgggaga ttgaagattt  
 721 ctgttgaaac ttacactgtt tcactcagc tttgatggt actgatgagt ctgatctag  
 781 atacaggact ggttccctcc ttagtttcaa agtgtctcat tctcagagta aaataggcac  
 841 cattgcttaa aagaaagtta actgacttca ctaggcattg tgatgtttag gggcaaacat  
 901 cacaaaatgt aatttaatgc ctgcccatta gagaagtatt taccaggaga aggtggtggc  
 961 attttgcct cctagtaagt caggacagct tgtatgtaag gaggtttata taagtaattc  
 1021 agtgggaatt cgacataatc gtttaatttt aagaaggcat tggcatctgc tttaatgga  
 1081 tgtataatac atccattcta catccgtagc ggttggtgac ttgtctgctt cctgctttgg  
 1141 gaagactgag gcacccgtga ggcagggaca agtcttctc ctcttgaga cccagtgcc  
 1201 tgcacatcat gagccttcag tcagggtttg tcagaggaaac aaaccagggg acactttgtt  
 1261 agaaagtgtc tagagggtct gcctctattt ttgtggggg gtgggagagg ggaccttaaa  
 1321 atgtgtacag tgaacaaatg tctaaaggg aatcattttt gtaggaagca tttttataa  
 1381 ttttctaagt cgtgcacttt ctccgtccac tctgttgaa gtgctgtttt attactgttt  
 1441 ctaaactagg attgacattc tacagttgtg ataatagcatt tttgtaact tgccatccgc  
 1501 acagaaaata cgagaaaatc tgcattgttg attatagat taatggacaa ataagttttt  
 1561 gctaaatgtg agtatttctg ttctttttt taaatatgtg acattctga ttgatttggg  
 1621 ttttttgtt gttgtgttt ttgtttgtt ttgtttttt ggatggagkc tcactctgt  
 1681 caccaggct ggagtgcagt ggcgccatct cggctcactg caacctctgc ctctgagtt  
 1741 cagtaatcc tctgagtag ctgggattac aggtgcctgc caccacgctg gccattttt  
 1801 gtacttttag tagagacagt gtttcgcat gttggccagg ctggtttcaa actcctgacc  
 1861 tcaggtgatc cgcccacctc agcctcccaa aatggtggga ttacaggtgt gtgggccacc  
 1921 gtgcctggct gattcagcat ttttatcag gcaggaccag gtggacttcc acctccagcc  
 1981 tctgtccta ccaatggatt catggagtag cctggactgt ttcagattt tctaaatgta  
 2041 caaattctta taggctagac ttgattcat taactcaat tcaatgcttc tatcagactc  
 2101 agtttttgt aactaataga tttttttt cactttgtt ctactcttc ctaatatgt  
 2161 ttttaaaaa atctcccag tagagaaaca ttggaaaag acagaaaact aaaaaggaag  
 2221 aaaaagatc cctattagat acacttctta aatacaatca cattaacatt ttgagctatt  
 2281 tcttccagc ctttttaggg cagattttgg ttggtttta catagttgag attgtactgt  
 2341 tcatacagtt ttataccctt ttcatthaa cttataact taaatattgc tctatgttag  
 2401 tataagcttt tcacaaacat tagtatagtc tccctttat aattaatgtt tgtgggtatt  
 2461 tcttggcatg catctttaat tcttatact agccttggg cacaattcct gtgctcaaaa  
 2521 atgagagtga ttgcttggcat ggtggctccc gcctgtaate ccagtacttt gggaagccaa  
 2581 ggtaagagga ttgcttgagc ccagaacttc aagatgagcc tgggctcata gtgagaaccc  
 2641 gtctatacaa aaaattttta aaaatagca tggcggcaca catctgtaat cctagctact  
 2701 tggcaggctg aggtgagaag atcattggag ttaggaatt ggaggcggca gtgagtcagt

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2761 agtatgccgc tgcactccag cctgggggac agagcaagac cctgcctcaa aaaaaaaaaa  
2821 aaaaaaaatt caggccggga atggtggttc acgcctgtaa tcccagcact ttggggggtc  
2881 gaggtgggca gatcacctga ggtcaggagt tcgagaccag cctggccaac atggtaaaac  
2941 cccatttcta ctaaaaata caagaattag ctgggtgtgg tggcgcacgc ctgtaacct  
3001 agctactcag gaggtcagg caggagaatc acttgacccc aggaggcgaa gattgcagtg  
3061 agctgataac gcaccattgt actccagcct gtgtgacaga gcaatctct tgtcccaaaa  
3121 aaaaaaaaaa tcaaatcag agtgaagtga atgagacact ccagttttcc ttctactccg  
3181 aattttagct cctccttca acattcaaca aatagctttt tttttttt tttttttg  
3241 gggatggagt ctccctctgt tggcaggct ggagtgcaga ggtgcgatct ctgctcacta  
3301 caagctctgc ctcccagatt caagtattc tcttggtca cctcctgag ctgggattac  
3361 aggcgcctgc caccatgcct ggctaattt gtgttttag tggagacggg gtttcacat  
3421 gttgtccagg atggtctga tctcctgacc ttgtgatcca cccacctcag cctcccaag  
3481 tgggtgggatt acaggtgtga gccaccgct ccagccagct ttattttt tttaagctg  
3541 tctttgtgc aaaatgatag tcatgtctc tctgttaaa acctgcaggc cgagcacagt  
3601 ggctcatgcc tgtaatccca gcattttggg agaccaaggc ggatggatca cctgaggtca  
3661 ggagctcaag accagcctgg ctaacatgg gaaacctcat ctccactaa aatacaaaaa  
3721 ttgccggccg cggcggctca tgcctgtaac cccagcactt tgggaggcct aggcgggtg  
3781 atcacgacgt caggaaatcg agaccatct ggctaacacg ggtgaaacc cgtctctatt  
3841 aaaaaataga aaaaattagg cggcggtgtt ggtgagcgcc ttagtccca gctactcag  
3901 agcctgaggc aggagaatgg catgaacctg gaaggtggag ctgacagtga gctgagatgg  
3961 tgccactgca ctctaacctg ggcgacagag tgagactccg tctcaaaaa aaaaacaaaa  
4021 accaaaactt atccaggtgt ggcggtgggc gcctgtgagg caggcgaatc tttgaaccc  
4081 gggaggcgga ggttgacagt agccaagatc acaccattgc actccagcct gggaacaag  
4141 agtgaaatc catctcaaaa ccaaatttc aaaaaaaaaa catgccgctt gactactgtg  
4201 ttttggtgt tgtccaagga aaattaaaac ctgtagcatg aataatgtt gtttcattt  
4261 cgaatctgt gaattgatta aatataatgc tcttaagaga cggtagaatt cctatttcaa  
4321 gttttttt tttgtttt ttttaagct gtttttaac acattaaatg gtgctgagta  
4381 aaggaaatag gcagggtgtg ttgtgtgtg ttttaactag gcgttctct ctacagagat  
4441 ttgaaacct gtttacataa agcccaaga tgggaaggag atccaaacat aagccaccag  
4501 cctcattcca agtctctct cttccaacc ctggatttt ttttttatt taacattgtt  
4561 tcttttagct ttattttct tataaaagaa atgtatcact ataaaaaatt acacactaca  
4621 gaaaaatatt aagaagaaaa acattcacat cggaaacaaa gttttttccc atgaaaacag  
4681 aacccaaaag ggtaagtgt tagtatttca ccagcaatta tgttgagaat aaggccaggc  
4741 gaggtggctc acgcctgtaa tctcagcact ttgggaggcc agggcaggca gatcatctga  
4801 ggtcaggagt ttgagaccag cctggccaac atggtgaaac cctatctcta ctaaaatta  
4861 aa

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**D21254 Human mRNA for OB-Cadherin-1**

1 cgcggagaga tgccgcgggg gccgctcgca gccgccgtg acttgtgaat gggaccggga  
 61 ctggggccgg gactgacacc gcagcgcttg cctgcgcca gggactggcg gctcggaggt  
 121 tgcgtccacc ctcaagggcc ccagaaatca ctgtgtttc agctcagcgg cctgtgaca  
 181 ttccttcgtg ttgtcatttg ttgagtgacc aatcagatgg gtggagtgtg ttacagaaat  
 241 tggcagcaag tatccaatgg gtgaagaaga agctaactgg ggacgtgggc agccctgacg  
 301 tgatgagtc aaccagcaga gacattccat cccaagagag gtctgcgtga cgcgtccggg  
 361 aggccaccct cagcaagacc accgtacagt tgggtgaagg ggtgacagct gcattctcct  
 421 gtgcctacca cgtaacaaa aatgaaggag aactactgtt tacaagccgc cctggtgtgc  
 481 ctgggcatgc tgtgccacag ccatgccttt gcccagagc ggcgggggca cctgcggccc  
 541 tccttccatg ggcacatga gaagggaag gaggggcagg tgctacagcg ctccaagcgt  
 601 ggctgggtct ggaaccagtt ctctgtgata gaggagtaca ccgggcctga cccgtgctt  
 661 gtgggcaggc ttattcaga tattgactct ggtgatggga acattaaata cattctctca  
 721 ggggaaggag ctggaacct tttgtgatt gatgacaaat cagggaacat tcatgccacc  
 781 aagcgttgg atcgagaaga gagagcccag tacacgttga tggctcaggc ggtggacagg  
 841 gacaccaat gccactgga gccaccgtcg gaattcattg tcaaggtcca ggacattaat  
 901 gacaaccctc cggagttcct gcacgagacc tatcatgcca acgtgcctga gaggtccaat  
 961 gtgggaacgt cagtaatcca ggtgacagct tcagatgcag atgacccac ttatggaat  
 1021 agcgccaagt tagtgtacag tatcctcga ggacaacct attttcggg ggaagcacag  
 1081 acaggtatca tcagaacagc cctaccaac atggacaggg aggccaagga ggagtaccac  
 1141 gtgtgatcc aggccaagga catgggtgga catatgggcg gactctcagg gacaaccaa  
 1201 gtgacgatca cactgaccga tgtcaatgac aaccaccaa agttccgca gagcgatac  
 1261 cagatatctg tgcagaagc agccgtccct ggggaggaag taggaagagt gaaagctaaa  
 1321 gatccagaca ttggagaaaa tggcttagtc acatacaata ttgtgatgg agatggtatg  
 1381 gaatcgttg aaatcacaa ggactatgaa acacaggagg ggtgataaa gctgaaaaag  
 1441 cctgtgatg ttgaaacaa aagagcctat agcttgaagg tagaggcagc caacgtgcac  
 1501 atcgaccgga agtttatcag caatggccct tcaaggaca ctgtgaccgt caagatcgca  
 1561 gtagaagatg ctgatgagcc ccctatgtt ttggcccaa gttacatcca cgaagtcaa  
 1621 gaaatgcag ctgctggcac cgtggttggg agagtgcag ccaaagacc tgatgctgcc  
 1681 aacagccgga taaggtatc catcgatcgt cactgacc tcgacagatt ttactatt  
 1741 aatccagagg atgttttat taaaactaca aaacctctgg atagagagga aacagcctgg  
 1801 ctcaacatca ctgtcttgc agcagaaatc cacaatcggc atcaggaagc caaagtcca  
 1861 gtggccatta ggtccttga tgtcaacgat aatgctcca agtttctgc ccctatgaa  
 1921 ggtttcatct gtgagagtg tcagaccaag ccacttcca accagccaat tgtacaatt  
 1981 agtgcatag acaaggatga cacggccaat ggaccaagat ttatcttcag cctacccct  
 2041 gaaatcattc acaatccaaa ttccacagtc agagacaacc gagataaac agcaggcgtg  
 2101 tacgcccggc gtggagggtt cagtcggcag aagcaggact tgtacctct gccatagtg  
 2161 atcagcgatg gcggcatccc gccatgagt agcaccaaca cctcaccat caaagtctgc  
 2221 ggtgctgacg tgaacggggc actgctctcc tgcaacgcag aggcctacat tctgaacgcc  
 2281 ggctgagca caggcgccct gatcgccatc ctgcctgca tctcattct cctggtcatt  
 2341 gtagtattgt ttgtgacct gagaaggcaa aagaagaac cactcattgt cttgaggaa  
 2401 gaagatgtcc gtgagaacat cactactat gatgatgaag ggggtgggga agaagacaca  
 2461 gaagcctttg atattgccac ctccagaat cctgatggtg tcaatggatt tatccccgc  
 2521 aaagacatca aacctgagta tcagtacatg cctagacctg ggctccggcc agcgcccaac  
 2581 agcgtggatg tcgatgactt catcaacag agaatacagg aggcagacaa tgacccacg  
 2641 gctctctctt atgactcat tcaaatctac ggttatgaag gcaggggctc agtggccggg  
 2701 tccctgagct ccttagagtc ggccaccaca gattcagact tggactatga ttatctacg  
 2761 aactggggac ctctgtttta gaaactagca gatttgtatg gtccaaaaga cacttttgat

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2821 gacgattctt aacaataacg atacaaattt ggccctaaga actgtgtctg gcgttctcaa  
2881 gaatctagaa gatgtgtaaa caggtatttt tttaaataca ggaaaggctc atttaaaaca  
2941 ggcaaagttt tacagagagg atacatttaa taaaactgcg aggacatcaa agtggtaaat  
3001 actgtgaaat acctttctc acaaaaaggc aaatattgaa gttgtttatc aacttcgcta  
3061 gaaaaaaaaa acactggca taaaaatat ttaagtgaag gagaagtcta acgctgaact  
3121 gacaatgaag ggaaattgtt tatgtgttat gaacatccaa gtctttctc tttttaagt  
3181 tgtcaaagaa gcttcacaa aattagaaag gacaacagtt ctgagctgta atttcgcctt  
3241 aaactctgga cactctatat gtagtgcatt tttaaactg aaatatataa tattcagcca  
3301 gcttaaacc atacaatgta tgtacaatac aatgtacaat tatgtctctt gagcatcaat  
3361 cttgttactg ctgattcttg taaatctttt tgcttctact tcatcttaa actaatcgt  
3421 gccagatata actgtcttgt ttcagtga gacgccctat ttctatgtca ttttaagt  
3481 atctatttgt acaattttaa agttcttatt ttagtatata tataaatatc agtattctga  
3541 catgtaagaa aatgttacgg catcacactt atattttatg aacattgtac tgttgcttta  
3601 atatgagctt caatataaga agcaatcttt gaaataaaaa aagatttttt tttaaaaaaa  
3661 a

**Figure 24. (Page 34 of 46)****D21255 Human mRNA for OB-cadherin-2**

1 acaggccccg gacgtcccc tcagctggcg gcggccgcgg agagatgccg cggggggccgc  
 61 tcgcagccgc cgctgacttg tgaatgggac cgggactggg gccgggactg acaccgcagc  
 121 gcttgccctg cgccagggac tggcggctcg gaggttgcgt ccaccctcaa gggccccaga  
 181 aatcactgtg ttccagctc agcggccctg tgacattcct tcgtgtgtc attgttgag  
 241 tgaccaatca gatgggtgga gtgtgttaca gaaattggca gcaagtatcc aatgggtgaa  
 301 gaagaagcta actggggacg tgggcagccc tgactgatg agtcaacca gcagagacat  
 361 tccatcccaa gagaggtctg cgtgacgcgt cggggaggcc accctcagca agaccaccgt  
 421 acagttggtg gaaggggtga cagctgcatt ctcctgtgcc taccacgtaa caaaaatga  
 481 aggagaacta ctgtttacaa gccgccctgg tgtgcctggg catgctgtgc cacagccatg  
 541 cctttgcccc agagcggcgg gggcacctgc ggccctcctt ccatgggcac catgagaagg  
 601 gcaaggaggg gcaggtgcta cagcgtcca agcgtggctg ggtctggaac cagtcttcg  
 661 tgatagagga gtacaccggg cctgaccccg tgcttgggg caggttcat tcagatattg  
 721 actctgtga tgggaacatt aaatacattc tctcagggga aggagctgga accattttg  
 781 tgattgatga caaatcaggg aacattcatg ccaccaagac gttggatcga gaagagagag  
 841 cccagtacac gttgatggct caggcgggtg acagggacac caatcgcca ctggagccac  
 901 cgtcggaatt cattgtcaag gtccaggaca ttaatgacaa cctccggag ttcctgcacg  
 961 agacctatca tgccaactg cctgagaggt ccaatgtggg aacgtcagta atccaggtga  
 1021 cagcttcaga tcagatgac ccacttatg gaaatagcgc caagttagtg tacagtatcc  
 1081 tcgaaggaca accctatatt tcggtggaag cacagacagg tatcatcaga acagccctac  
 1141 ccaacatgga caggagggcc aaggaggagt accacgtggt gatccaggcc aaggacatgg  
 1201 gtggacatat gggcggactc tcagggacaa ccaaagtac gatcacactg accgatgtca  
 1261 atgacaaccc accaaagttt ccgcagagcg tataccagat atctgtgtca gaagcagccg  
 1321 tccctgggga ggaagtagga agagtgaag ctaaatgacc agacattgga gaaaatggct  
 1381 tagtcacata caatattgtt gatggagatg gtatggaatc gtttgaaatc acaacggact  
 1441 atgaacaca ggagggggtg ataaagtga aaaagcctgt agattttgaa accaaaagag  
 1501 cctatagctt gaaggtagag gcagccaacg tgcacatcga ccgaagtgt atcagcaatg  
 1561 gccctttcaa ggacactgtg accgtcaaga tcgacgtaga agatgtgat gagcccccta  
 1621 tgttcttggc ccaagttaac atccacgaag tccaagaaaa tgcagctgct ggcaccgtgg  
 1681 ttgggagagt gcatgcaaaa gaccctgatg ctgccaacag ccgataagg tattccatcg  
 1741 atcgtcacac tgacctgac agatttttca ctattaatcc agaggatggt ttattaaaa  
 1801 ctacaaaacc tctgataga gaggaacag cctggctcaa catcactgtc ttgcagcag  
 1861 aaatccacaa tcggcatcag gaagccaaag tccagtggc cattagggtc ctgatgtca  
 1921 acgataatgc tccaagtgt gctgccctt atgaaggtt catctgtgag agtgatcaga  
 1981 ccaagccact ttcaaccag ccaattgtta caattagtgc agatgacaag gatgacacgg  
 2041 ccaatggacc aagatttate ttacgcctac ccctgaaat cattcacaat ccaaattca  
 2101 cagtcagaga caaccgagat aacacagcag gcgtgtacgc ccggcgtgga ggttcagtc  
 2161 ggcagaagca ggactgtac cttctgcca tagtgatcag cgatggcggc atcccgcca  
 2221 tgatagcac caacaccctc accatcaaag tctgcgggtg cgacgtgaac ggggcactgc  
 2281 tctcctgcaa cgcagaggcc tacattctga acgccggcct gagcacaggc gccctgatcg  
 2341 ccatcctgcg ctgcatctc attcctctgg gttgccaag cttaatggaa cccccctc  
 2401 ccagggaaga catgagattg cttatctgg gcttcagct gatgctattt tctatgtta  
 2461 aagtaaacag aagattttgt cttctggggg tctttataaa acttcttctc ctctatgtg  
 2521 tggctacaga gactccaacc acacttacgt catttagta ttgtttgta ccttgagaag  
 2581 gcaaaagaaa gaaccactca ttgtcttga ggaagaagat gtccgtgaga acatcattac  
 2641 ttatgatgat gaaggggggtg gggaagaaga cacagaagcc ttgatattg ccaccctca  
 2701 gaatcctgat ggtatcaatg gatttatccc ccgcaaagac atcaaacctg agtatcagta  
 2761 catgcctaga cctgggctcc ggccagcgc caacagcgtg gatgtcgtg acttcatcaa



**Figure 24. (Page 35 of 46)**

2821 cacgagaata caggaggcag acaatgaccc cacggctcct ccttatgact ccattcaa  
2881 ctacggttat gaaggcaggg gtcagtggc cgggtccctg agctccctag agtcggccac  
2941 cacagattca gacttgact atgattatct acagaactgg ggacctcgtt ttaagaaact  
3001 agcagatttg tatggttcca aagacacttt tgatgacgat tcttaacaat aacgatacaa  
3061 atttggcctt aagaactgtg tctggcggtc tcaagaatct agaagatgtg taaacaggta  
3121 ttttttaaa tcaaggaaag gtcatttaa aacaggcaaa gttttacaga gaggatacat  
3181 ttaataaaac tgcgaggaca tcaaagtggt aaatactgtg aaataccttt tctcacaaaa  
3241 aggcaaatat tgaagttgtt tatcaacttc gctagaaaaa aaaaacactt ggcatacaaa  
3301 atatttaagt gaaggagaag tctaacgctg aactgacaat gaagggaaat tgtttatgtg  
3361 ttatgaacat ccaagtcttt cttcttttt aagttgtcaa agaagcttcc acaaaattag  
3421 aaaggacaac agttctgagc tgtaatttcg ccttaaacctc tggacactct atatgtagt  
3481 catttttaaa cttgaaatat ataatttca gccagcttaa acccatacaa tgtatgtaca  
3541 atacaatgta caattatgtc tcttgagcat caatcttgtt actgctgatt cttgtaaate  
3601 tttttgctc tactttctc ttaactaat acgtgccaga tataactgtc ttgttcagt  
3661 gagagacgcc ctatttctat gtcattttta atgtatctat ttgtacaatt ttaaagttct  
3721 tattttagta tacatataaa tatcagtatt ctgacatgta agaaaatgtt acggcatcac  
3781 acttatattt tatgaacatt gtactgtgc tttaatatga gcttcaatat aagaagcaat  
3841 ctttgaata aaaaaagatt tttttt

**Figure 24. (Page 36 of 46)****NM\_014935 Homo sapiens phosphoinositol 3-phosphate-binding protein-3 (PEPP)**

1 gctggatcct gcagtaacca caacagcatc ctctccctgc gccagggacc tgccagccgg  
 61 agagatgact gattagatca gattagatcc ggagccccgc tctgcagaag ggggccccag  
 121 gggcggggga ggaggacccc agctggcctg agctgggggg aggggtgcct tggggctcgc  
 181 agagttagag cttccagcg cggggatcac acctcagaag ccgccacaat gaaagacgga  
 241 acacatttct acaccagtg actggccagg tcccagagga aaacaaaaaa ttgacttga  
 301 aaatatgcac ctggacatg tccaataaaa caggtgggaa acgcccggct accaccaaca  
 361 gtgacatacc caaccacaac atggtgtccg aggtccctcc agagcggccc agcgtccggg  
 421 caactcgcac agcccgcaa gccatgcct ttggcaagcg ctcacactcc atgaagcgga  
 481 acccaatgc acctgtacc aaggcgggct ggctcttcaa acaggccagc tccgggggta  
 541 agcagtggaa caagcgtgg ttcgtcctgg tggatcgtg cctctctac tataaagatg  
 601 agaaggaaga gattatcctg ggcagcatcc cctcctgag ctccgggta gccgcagtgc  
 661 agccctcaga caacatcagc cggaacaca cgtttaaggc tgagcatgcc ggggtccgca  
 721 cctacttctt cagtcccgag agccccgagg agcaagaggc ctggatccag gccatggggg  
 781 aggtgtctcg agtacagatc cctccagccc agaagtcagt gccccaagct gtgcggcaca  
 841 gccatgagaa gccagactcg gagaacgtcc caccagcaa gcaccaccag cagccacccc  
 901 acaacagcct cctaagcct gagccagagg ccaagactcg aggggagggt gatggccgag  
 961 gctgtgagaa ggagagaga aggcctgaga ggccagaagt caagaaagag cctccgggta  
 1021 aagccaatgg cctccagct ggaccggagc cagcctcaga gccgggcagc ccttccccg  
 1081 agggcccaag agtgccaggg ggtggggaac agcctgccca gcccaatggc tggcagtacc  
 1141 actcccaag ccggccaggg agcacagctt tccctctca ggatggagag actgggggac  
 1201 accggcgagg tttccacca cgcaccaacc ctgacaaaat tgcccagcgc aagagctcca  
 1261 tgaaccagct tcagcagtgg gtgaatctgc gccggggggg acccccgcct gaagacctc  
 1321 ggagtccttc taggttctat cctgtgtctc gcagggtccc tgagtactat ggcccctact  
 1381 cctccagta cccgatgat tatcagtact acccgccagg agtgcggccg gagagcatct  
 1441 gttccatgcc ggccatgat cggatcagcc cggcctgggc cctggaggac aagcgccatg  
 1501 cctccgcaa tgggggtggc cctgcctacc agctgcgaga gtggaaggag cccgccagct  
 1561 acgggcggca ggatgccacc gtctggatcc caagcccctc ccggcagcca gtctattatg  
 1621 atgagctgga tgcgcctct agtcccctgc gccgcctgtc cctgcagccc cgtcccact  
 1681 ctgtgccccg ctacccagc cagggtcct acagcgtgc ccgcattac tcccctgtcc  
 1741 gctcaccagc tgcccgctt gagcggctgc cacctcagc tgaggacatc tatgttgacc  
 1801 ctgtgccta tgtgatgagg cgtccatca gctccccc aaagtcccca taccagaag  
 1861 tgttcggga cagcctcac acctacaagt taaacagca agacacagat aagctgtctg  
 1921 gaaaattgtg tgagcagaac aaggtgtga gggagcagga ccggctggtg cagcagctcc  
 1981 gagctgagaa ggagagcctg gaaagtgcct tgatggggac ccaccaggag ctggagatgt  
 2041 ttggaagcca gccgcctac ccagaaaagc tgcgacaaa aaaggattca ctgcagaacc  
 2101 agctcatcaa catccgctg gagctgtctc aggcgaccac gccctgaca aacagcacca  
 2161 tagagtatga gcacctgag tctgaggtct ctgcctgca cgtgacctc tgggagcagc  
 2221 tcaatttga caccagaat gaggtgtga accggcaaat ccaaaaggag atctggagga  
 2281 tccaggacgt gatggagggg ctgaggaaga acaacccctc ccggggcacg gacaccgcca  
 2341 agcacagagg aggaattggc cctcagcca cctacagctc caacagccc gccagcccc  
 2401 tcagctctgc cagcctacc agcccctga gccctttc actggtgtcg ggctctcagg  
 2461 ggtcccccac caagcctggc tccaacgagc ccaaggcaaa ctatgaacaa agcaagaaag  
 2521 acccccacca gacattgcc ctggacacc ccagagacat cagccttgtg cccaccaggc  
 2581 aagaggtaga ggcagagaag caggcagctc tcaacaaagt tggcgtgtg ccccctcgga  
 2641 caaaatgcc cactgatgat gaggtgacct catcagcagt ggtaagaagg aatgccagt  
 2701 ggctaccaa tggactctcc tcccaggaac gccccaagag tgctgtgtt cctggcgagg  
 2761 ggaaggtcaa gatgagcgtg gaggagcaga ttgaccgaat gcggcgccac cagagtggct

**Figure 24. (Page 37 of 46)**

2821 ccatgaagga gaagcggagg agcctgcagc tcccggccag cccggccccc gacccagtc  
2881 cccggccagc ctacaaagt gtgcgccgcc accgcagcat ccacgagga gacatctcca  
2941 acctggaggc agccctgcgg gcagaggagc ctggcgggca tgcctacgag acacccggg  
3001 aggaaattgc cggcttcgc aaaatggagc tagagcccca gcattatgac gtggacatca  
3061 ataaggagct ctccactcca gacaaagtcc tcacccctga acggtacatt gacctggagc  
3121 ctgacactcc cctgagccct gaggagtga aggagaagca gaagaagggtg gagaggatca  
3181 agacactcat tgccaaatcc agtatgcaga acgtgggtgcc catcggcgag ggggactctg  
3241 tggacgtgcc ccaggactca gagagccagc tgcaggagca ggagaagcgg attgaaatct  
3301 cctgcgccct ggcgaccgag gcctcccgca ggggcccgcac gctgtctgtg caatgtgcca  
3361 ccccaagccc tcccactcc cctgttccc cggtcctcc agcaaacccc ctgtcgtctg  
3421 aatccccacg gggcgccgac agcagctata ccatgcgggt ctgagctctg actgcaagcc  
3481 ctgggtgagg ccaatgtgt gaagctccac agagccacat tctgaagccg tcctctgccc  
3541 acctgaggtc ctggctcccc accctggccc cctgcccctg cactcccatg ggaatgccgc  
3601 agggagccag gctggggcca tgggctgtctg ccaggagacc gtggatacct cagtgtccac  
3661 acaccacca tcccagccc tggagccatc actactaca ccgtggctct gggccagggc  
3721 ctgagatgac agtggggagc accatcctca ttaatgtcca agtcacaggg agcctcagcc  
3781 ttgccctggc tggggtgtg gtgactccag tggaaacatc cctgatgggg gacatgccgt  
3841 ggtggagaac acacctgttg ctatcttatg ttaggactag aggtgaagag gagatggaca  
3901 ctgcctctgg agccagcctg acaccaagga cagcacttgt catcatccct atcctcgtca  
3961 gccccacct gctgcctcag ctggaccag ggcttgaca caaacccagt gctttgcta  
4021 tgggtgctcg ctggggtccg gtggagactg accaccctgc ttgagccaaa gacaaggatga  
4081 tgagagatgg ggagaggcca ttggtccca gaggaacag tgctggctgt ggctagagaa  
4141 cagcaggtct gtgcagtgtc ttagggcagg ttgggaagg tagcagagag agagagacag  
4201 aaagagagag agagagagag agagagagag agagagagag agagagatcc tcagagtgga  
4261 aggaggggga agcagcagga cacattggca agtcaagcag gaaggaggga gatggaaagg  
4321 ggatatcaga ttggtttccc ccggtggagc cttaggttag tgcccagtc agtgccagac  
4381 tgtctctct gtctctccca cctcatccct aggaggaccc accagtggag cacatgcagc  
4441 ctacgtggag atgcttggtg tggggatctg ggtgaagggg gttagtagc gactgcctgg  
4501 gagatggctg ttagttagtc tgcgcctgt gtctgcctcg ccatcctggg gtaaggggca  
4561 gagagaagga ctgtcttat gtagggtgtg gtcagccttg gggccttacc taccagttc  
4621 catgatattt ctggccctgt tcccctgga atgtgcagtg ggccagctga gactacgcct  
4681 ttaggagggg ggatgaggcc ttaatctggg aggcctatcc ccctatccca ggcatcccag  
4741 acgaggactg gctgaggcta ggcgtctca tgatccacct gccccgggag ggcagcgggg  
4801 aagacagaga aaagcaaaca cattcctcct cagctccacc cacctggaga cgaatgtagc  
4861 cagagaggag gaaggaggga aactgaaaac accgtggccc ctggccttc tctctgctag  
4921 agttgccgt cagaggttc agctgactt ccagcggtec caagaacacc tactaattcc  
4981 tctccactcc tcatggctg ggacagttac tggttcatat gcaagtaaag atgacaattt  
5041 actcaac

**Figure 24. (Page 38 of 46)****M61906 Human PI3-kinase, p85 subunit**

1 tacaaccagg ctcaactgtt gcatggtagc agatttgcaa acatgagtgc tgaggggtac  
 61 cagtacagag cgctgtatga ttataaaaag gaaagagaag aagatattga ctgcacttg  
 121 ggtgacatat tgactgtgaa taaaggggtcc ttagtagctc ttggattcag tgatggacag  
 181 gaagccaggc ctgaagaaat tggctggta aatggctata atgaaaccac aggggaaagg  
 241 ggggactttc cgggaactta cgtagaatat attggaagga aaaaaatctc gcctcccaca  
 301 ccaaagcccc ggccacctcg gcctcttctt gttgcaccag gttcttcgaa aactgaagca  
 361 gatgttgaac aacaagcttt gactctccc gactttgcag agcagtttgc cctcctgac  
 421 attgccccgc ctcttcttat caagctcgtg gaagccattg aaaagaaagg tctggaatgt  
 481 tcaactctat acagaacaca gagctccagc aacctggcag aattacgaca gcttcttgat  
 541 tgtgatacac cctccgtgga cttggaaatg atcagatgtc acgttttggc tgacgcttc  
 601 aaacgctatc tcttggaact accaaatctt gtcattccag cagccgttta cagtgaatg  
 661 atttcttag ctccagaagt acaaagctcc gaagaatata ttcagctatt gaagaagctt  
 721 attaggtcgc ctacataacc tcatcagat tggcttacgc ttcagtattt gttaaaacat  
 781 ttcttcaagc tctctcaaac ctccagcaaa aatctgttga atgcaagagt actctctgaa  
 841 attttcagcc ctatgctttt cagattctca gcagccagct ctgataatac tgaaaacctc  
 901 ataaaagtta tagaaatttt aatctcaact gaatggaatg aacgacagcc tgcaccagca  
 961 ctgcctccta aaccacaaaa acctactact gtagccaaca acggtatgaa taacaatatg  
 1021 tctttacaaa atgtcgaatg ttaactgggga gatattctga gggaagaagt gaatgaaaaa  
 1081 cttcgagata cagcagacgg gacctttttg gtacgagatg cgtctactaa aatgcatggt  
 1141 gattatactc ttacactaag gaaaggggga aataacaaat taatcaaaat atttcatcga  
 1201 gatgggaaat atggcttctc tgaccatta accttcagtt ctgtggttga attaataaac  
 1261 cactaccgga atgaatctct agctcagat aatcccaaat tggatgtgaa attactttat  
 1321 ccagtatcca aataccaaca ggatcaagtt gtcaaagaag ataatttga agctgtaggg  
 1381 aaaaaattac atgaatataa cactcagttt caagaaaaaa gtcgagaata tgatagatta  
 1441 tatgaagaat ataccgcac atcccaggaa atccaaatga aaaggacagc tattgaagca  
 1501 ttaattgaaa ccataaaaaa atttgaagaa cagtgccaga ccaagagcg gtacagcaaa  
 1561 gaatacatag aaaagttaa acgtgaaggc aatgagaaag aaatacaaag gattatgcat  
 1621 aattatgata agttgaagtc tgaatcagt gaaattattg acagtagaag aagattggaa  
 1681 gaagacttga agaagcaggc agctgagat cgagaaattg acaaacgtat gaacagcatt  
 1741 aaaccagacc ttatccagct gagaagacg agagaccaat acctgatgtg gttgactcaa  
 1801 aaaggtgttc ggcaaaagaa gttgaacgag tggttgggca atgaaaacac tgaagacca  
 1861 tattactcgg tggaagatga tgaagattg ccccatcatg atgagaagac atggaatgtt  
 1921 ggaagcagca accgaaacaa agctgaaaac ctgttgcgag ggaagcgaga tggcactttt  
 1981 ctgtccggg agagcagtaa acagggctgc tatgcctgct ctgtagtgtt ggacggcgaa  
 2041 gtaaagcatt gtgtcataaa caaacagca actggctatg gctttgccga gccctataac  
 2101 ttgtacagct ctctgaaaga actggtgcta cattaccaac acacctccct tgtgcagcac  
 2161 aacgactccc tcaatgtcac actagcctac ccagtatatg cacagcagag gcgatgaagc  
 2221 gcttactctt tgatcttct cctgaagtc agccacctg aggcctctgg aaagcaaagg  
 2281 gctcctctcc agtctgatct gtgaattgag ctgcagaaac gaagccatct ttcttggat  
 2341 gggactagag ctttcttca caaaaaagaa gtagggggag acatgcagcc taaggctgta  
 2401 tgatgaccac acgttcttaa gctggagtgc ttatccctt ttttcttt ttctttggt  
 2461 ttaatttaaa gccacaacca catacaacac aaagagaaaa agaaatgcaa aaatctctgc  
 2521 gtgcagggac aaagaggcct ttaacctagg tcttgttaa tctttctga agctttacca  
 2581 gctgaaagt gggactctgg agagcggagg agagagaggc agaagaacc tggcctgaga  
 2641 aggtttgtc cagcctggt tagcctggat gttgctgtgc acggtggacc cagacacatc  
 2701 gcactgtgga ttatttcatt ttgtaacaaa tgaacgatat gtagcagaaa ggcacgtcca  
 2761 ctcaacagg acgctttggg agaatgtcag ttcagtgtg ttcagaagaa attctgtcat

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2821 agaaagtgcc agaaagtgtt taacttgtca aaaaacaaaa acccagcaac agaaaaatgg  
2881 agtttgaaa acaggactta aaatgacatt cagtatataa aatatgtaca taatattgga  
2941 tgactaacta tcaaatagat ggatttgtat caataccaaa tagcttctgt ttgttttgc  
3001 tgaaggctaa atcacagcg ctatgcaatt ctaattttc attaagttgt tattcagtt  
3061 ttaatgtac cttcagaata agcttcccca cccagtttt tgttgcttga aaatattgtt  
3121 gtcccggtt ttgttaata ttcattttg ttatccttt ttaaaaataa atgtacagga  
3181 tgccagtaaa aaaaaaatg gcttcagaat taaaactatg aaatattta cagttttct  
3241 tgtacagagt acttgctgtt agccaaggt taaaagtgc ataacagatt tttttggac  
3301 tgttttgtg ggcagtgcct gataagctc aaagctgctt tattcaataa aaaaaaac  
3361 cgaattcact gg

Figure 24. (Page 40 of 46)

**J05582 Human mucin 1**

1 ccgtccacc tctcaagcag ccagcgctg cctgaatctg ttctgcccc tccccacca  
61 ttaccacc accatgacac cgggcacca gtctcttc ttctgctgc tgcctcac  
121 agtgcttaca gttgtacag gttctgtca tgcaagctt accccaggtg gagaaaagga  
181 gacttcggt acccagagaa gttcagtcc cagctctact gagaagaatg ctgtgagtat  
241 gaccagcagc gtacttcca gccacagccc cggttcaggc tctccacca ctcagggaca  
301 ggatgtcact ctggccccgg ccacggaacc agcttcaggt tcagtgcca cctggggaca  
361 ggatgtcacc tcggccccag tcaccaggcc agccctgggc tccaccacc cggcagccca  
421 cgatgtcacc tcagccccgg acaacaagcc agccccgggc tccaccgcc cccagccca  
481 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
541 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
601 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
661 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
721 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
781 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
841 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
901 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
961 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
1021 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
1081 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
1141 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
1201 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
1261 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
1321 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
1381 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
1441 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
1501 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
1561 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
1621 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
1681 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
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2641 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
2701 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca  
2761 cgggtgtcacc tcggccccgg acaccaggcc ggccccgggc tccaccgcc cccagccca

**Figure 24. (Page 41 of 46)**

2821 cgggtgcacc tcggccccgg acaccaggcc ggccccgggc tccaccgccc cccagccca  
2881 tgggtgcacc tcggccccgg acaacaggcc cgccttgggc tccaccgccc ctccagtcca  
2941 caatgtcacc tcggcctcag gctctgcac aggtcagct totactctgg tgcacaacgg  
3001 cactctgcc agggctacca caaccccagc cagcaagagc actccattct caattcccag  
3061 ccaccactct gatactcta ccaccctgc cagccatagc accaagactg atgccagtag  
3121 cactcaccat agctcggtag ctctctcac ctctccaat cacagcactt ctccccagt  
3181 gtctactggg gtctctttct tttctgtc tttcacatt tcaaacctcc agtttaattc  
3241 ctctctggaa gatcccagca cgcactact ccaagagctg cagagagaca tttctgaaat  
3301 gttttgcag atttataaac aaggggggtt tctgggcctc tccaatatta agttcaggcc  
3361 aggatctgtg gtgttacaat tgactctggc ctccgagaa ggtaccatca atgtccacga  
3421 cgtggagaca cagttcaatc agtataaac ggaagcagcc tctcgatata acctgacgat  
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3541 gccaggctgg ggcacgcgc tctgggtgt ggtctgtgt ctggttgcgc tggccattgt  
3601 ctatctcatt gccttggctg tctgtcagt cgcgcgaaag aactacgggc agctggacat  
3661 ctttcagcc cgggatacct accatctat gacgcagtag cccacctacc acacctatgg  
3721 gcgctatgtg cccctagca gtaccgatc tagccctat gagaagggtt ctgcaggtaa  
3781 cgggtggcagc agcctctctt acacaaacc agcagtggca gccgttctg ccaactgta  
3841 gggcacgtcg ccgtgagct gagtggccag ccagtgccat tccactccac tcaggttctt  
3901 caggccagag cccctgcacc ctgttgggc tggtagctg ggagttcagg tgggctgctc  
3961 acagcctcct tcagaggccc caccaatttc tcggacactt ctcaagtgtt ggaagctcat  
4021 gtgggcccct gaggtcatg cctgggaagt gttgtggggg ctcccaggag gactggccca  
4081 gagagccctg agatagcggg gatcctgaac tggactgaat aaaacgtggt ctcccactg

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**M29366 Human Epidermal Growth Factor Receptor (ErbB3)**

1 accaatcgcc cagcgggtca ggtggctctt gcctcgatgt cctagcctag gggcccccg  
 61 gccggacttg gctgggctcc cttaccctc tgcggagtca tgaggcgcaa cgacgctctg  
 121 cagggtcctg gcttgctttt cagcctggcc cggggctccg aggtgggcaa ctctcaggca  
 181 gtgtgtcctg ggactctgaa tggcctgagt gtgaccggcg atgctgagaa ccaataccag  
 241 acactgtaca agctctacga gaggtgtgag gtggtgatgg ggaaccttga gattgtgctc  
 301 acgggacaca atgccgacct ctcttctcgt cagtggattc gagaagtgc aggctatgtc  
 361 ctctgggcca tgaatgaatt ctctactcta ccattgcccc acctccgcgt ggtgcgaggg  
 421 acccaggtct acgatgggaa gtttgccatc ttgctcatgt tgaactataa caccaactcc  
 481 agccacgctc tgcgccagct ccgcttgact cagtcaccg agattctgtc aggggggtgt  
 541 tatattgaga agaacgataa gctttgtcac atggacacaa ttgactggag ggacatcgtg  
 601 agggaccgag atgctgagat agtgggaag gacaatggca gaagctgtcc cccctgtcat  
 661 gaggtttgca agggggcagc ctggggctct ggatcagaag actgccagac attgaccaag  
 721 accatctgtg ctctcagtg taatggtcac tgccttgggc ccaaccccaa ccagtgtgc  
 781 catgatgagt gtgccggggg ctgctcaggc cctcaggaca cagactgctt tgcctgccgg  
 841 cacttcaatg acagtggagc ctgtgtacct cgtgtccac agcctctgt ctacaacaag  
 901 ctaactttcc agctggaacc caatccccac accaagtatc agtatggagg agtttgtga  
 961 gccagctgtc cccataactt tgtggtggat caaacatcct gtgtcagggc ctgtctctct  
 1021 gacaagatgg aagtataa aaatgggctc aagatgtgtg agccttgtgg gggactatgt  
 1081 cccaaagcct gtgagggaa aggctctggg agccgcttc agactgtgga ctgagcaaac  
 1141 attgatggat ttgtgaactg caccaagatc ctgggcaacc tggactttct gatcacggc  
 1201 ctcaatggag acccctggca caagatccct gccctggacc cagagaagct caatgtctc  
 1261 cggacagtac gggagatcac aggttacctg aacatccagt cctggccgcc ccacatgcac  
 1321 aacttcagt tttttccaa ttgacaacc attggaggca gaagcctcta caaccggggc  
 1381 ttctcattgt tgatcatgaa gaactgaat gtcacatctc tgggcttcg atccctgaag  
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 1741 gaatgttct cctgccacc ggaatgcaa ccatggagg gcactgccac atgcaatggc  
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 2341 agtggacggc agagtttca agctgtgaca gatcatatgc tggccattgg cagcctggac  
 2401 catgccaca ttgtaaggct gctgggacta tggccagggt catctctgca gctgtcact  
 2461 caatatttgc ctctgggtc tctgtggat catgtgagac aacaccgggg gcactgggg  
 2521 ccacagctgc tgcctaactg gggagtacaa attgccaagg gaatgtacta ccttgaggaa  
 2581 catggtatgg tgcatagaaa cctggctgcc cgaacgtgc tactcaagtc acccagtcag  
 2641 gttcaggtgg cagattttg tgtggctgac ctgtgcctc ctgatgataa gcagctgcta  
 2701 tacagtgagg ccaagactcc aattaagtgg atggcccttg agagtatcca ctttgggaaa  
 2761 tacacacacc agagtgtat ctggagctat ggtgtgacag ttgggagtt gatgacctc



**Figure 24. (Page 43 of 46)**

2821 ggggcagagc cctatgcagg gctacgattg gctgaagtac cagacctgct agagaagggg  
2881 gagcgggttg cacagcccca gatctgcaca attgatgtct acatgggtgat ggtcaagtgt  
2941 tggatgattg atgagaacat tcgccaacc tttaaagaac tagccaatga gttcaccagg  
3001 atggcccag acccaccag gtatctggtc ataaagagag agagtgggcc tggaatagcc  
3061 cctgggccag agccccatgg tctgacaaac aagaagctag aggaagtaga gctggagcca  
3121 gaactagacc tagacctaga cttggaagca gaggaggaca acctggcaac caccacactg  
3181 ggctccggcc tcagcctacc agttggaaca cttaatcggc cacgtgggag ccagagcctt  
3241 ttaagtccat catctggata catgcccag aaccagggtg atcttgggga gtcttgccag  
3301 gagtctgag ttctgggag cagtgaacgg tgcctccgct cagtctct acaccaatg  
3361 ccacggggat gcctggcatc agagtcatc gaggggcatg taacaggctc tgaggctgag  
3421 ctccaggaga aagtgtcaat gtgtagaagc cggagcagga gccggagccc acggccacgc  
3481 ggagatagcg cctaccattc ccagcgccac agtctgctga ctctgttac cccactctcc  
3541 ccacccgggt tagaggaaga ggatgtcaac ggttatgtca tgccagatac acacctcaa  
3601 ggtactccct cctccggga aggcaccctt tctcagtg gtcttagtgc tgcctgggt  
3661 actgaagaag aagatgaaga tgaggagtat gaatacatga accggaggag aaggcacagt  
3721 ccactcatc ccctaggcc aagtccctt gaggagctgg gttatagta catggatgtg  
3781 gggtcagacc tcagtgcctc tctgggcagc acacagagt gccactcca ccctgtacc  
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3901 gatggagggt gtcctggggg tgattatgca gccatggggg cctgcccagc atctgagcaa  
3961 gggatgaag agatgagagc ttctagggg cctggacatc agggcccca tgtccattat  
4021 ccccgccaa aaactctacg tagcttagag gctacagact ctgccttga taacctgat  
4081 tactggcata gcaggctttt cccaaggct aatgccaga gaacgtaact cctgctccct  
4141 gtggactca gggagcattt aatggcagct agtgcctta gagggtagcg tctctccct  
4201 attccctc tcctccagg cccagccctt ttccccagt cccagacaat tccattcaat  
4261 ctttgaggc tttaaacaat ttgacacaa aattcttatg gtatgtagcc agctgtgcac  
4321 ttctctct ttcccaacc caggaaagg ttctctatt ttgtgtgct tccagtcct  
4381 attcctcagc ttctcacag gactcctgg agatatgaag gattactct catatccct  
4441 cctctcaggc tctgactac ttggaactag gctcttatgt gtgcctttgt tcccatcag  
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4561 ctcttaacc ctagaaaga cagaagctta aaatctgtga agaaagagg taggagtaga  
4621 tattgattac tatcataatt cagcactta ctatgagcca ggcatacat taaactcac  
4681 ctacattatc tacttagtc ctttatcatc cttaaaacaa ttctgtgaca tacatattat  
4741 ctcattttac acaaaggga gtcgggcatg gtggctcatg cctgtaact cagcatttg  
4801 ggaggctgag gcagaaggat tacctgagc aaggagtgtg agaccagctt agccaacata  
4861 gtaagacccc catctctt

**Figure 24. (Page 44 of 46)****Homo sapiens gene for hepatitis C-associated microtubular aggregate protein p44****D28908 Exon 1 and 2**

1 gaattctgaa tataggacac gaatttatga tccttagcaa tgtgaagta gagaaggggt  
 61 ttattgtga aattgacaca ggttggttta tatcttataa atgaagtctc ctcattttcc  
 121 tgtggtcaga agagaggggg caagcagaaa agcagaggaa caaatttggg ggctaaaata  
 181 acattctaca taaggaacta tactacagta gaattaattg atagcaggga ttaagagatg  
 241 taaatgaatt tgagatacat attctagagg tagaatgtgc aatactttt gtatgtccat  
 301 atacagaaat tgggtgcatt ttccttaaataaaaaagattt ttaaaaagtc agtgagctgt  
 361 tatgttttct tccctctgac tcaattcct tgattcttct aatttttta atataaattt  
 421 actgtctaaa agctggatca gcttatgctc cttgttgag agaagttggc atgctgtcaa  
 481 gtgggctggg cacactgagt ttcagtttcc ttctctgag tctttgaagc tcaaggctg  
 541 ctgaataatt tccctctccc attttgtgcc tgcctagcta tccagacaga gcagctaccc  
 601 tcagctctag ctgatactac agacagtaca acaggtaaata gtcttctgc tttcatttt  
 661 tctagctag cattagtctc tctctgtctc tctcaggtga cagtgtccat tgcaatctca  
 721 gttttgttt taatttaaaa aacaataatt tatagtaaaa aattagctaa tgatttttt  
 781 gcttctgtt catccttgt tttgtcattt ttgtattat gtagagtata taagaggcat  
 841 aaatgcaaat ttataacta catattatct gtttttaatt attaatgga aaatatatat  
 901 gatttgccac tagatcaaga agtatggcag tgacaactcg ttgacatgg ttgcacgaaa  
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 1501 ctgaaacctg gatacagatt gtttgcataag agacaacat ggtcaataaa atgtatattt  
 1561 atgataagaa cccttaacgt aagatttatt ctcttagcac attttaagta c

**D28909 Exon 3**

1 gaattcactg atattcattc attcattcag ccaattattc gacaacttct aatctacatt  
 61 attctttgat tatttcccca gattcactgg atgaaagaaa gataaaaggg gtcattgagt  
 121 aagtcattgt ttttaagatt ctattactct ctcca

**Figure 24. (Page 45 of 46)****D28910      Exon 4**

1 ttgcgacct aacctcagtc aattgttaaa aacggtcattg tctaaacagg ctcaggaaga  
61 gcttactgtc tgccttgaga acttatgaac catatggatc cctgggtcaa caaatacgaa  
121 ttctctctct ggggtccaatt ggagctccca agtccagctt ttcaactca gtgaggtctg  
181 tttccaagg gcatgtaacg catcaggctt tgggtgggcac taatacaact gggatatctg  
241 agaaggtaag cacatttgag gccacctagc ctttgcttct ctgttcaaact caattatatt  
301 tcaaaagctt tt

**D28911      Exon 5**

1 ggccacctag cctttgcttc tctgttcaaa tcaattatat ttcaaaagcc tttgcagat  
61 caactttatt acatatagac ttcatctcaa ttataataa aaaatgaatc tttaaattg  
121 cttttctccc ctctacagta taggacatac tctattagag acgggaaaga tggcaaatac  
181 ctgccgttta ttctgtgtga ctactgggg ctgagtgaga aagaaggcgg cctgtgcagg  
241 gatgacatat tctatatctt gaacggtaac attcgtgata gataccagggt aatatttgac  
301 taatgagaaa ttataactga tttttaaact gcttattttt gtacaaatgt atcagcggtt  
361 atcttcttaa attatacttg ctcaagatcc ttgtctctt tttagatttt ttttcaaaa  
421 agaataaaaa catctcgagg gctcttc

**D28912      Exon 6**

1 ttgtgctcat aaatatttgt tgaattaata tcttgcttta tgtctacctt acagttaat  
61 cccatggaat caatcaaatt aaatcatcat gactacattg attccccatc gctgaaggac  
121 agaattcatt gtgtggcatt tgtatttgat gccagctcta ttcaatactt ctctctcag  
181 atgatatgaa agatcaaaaag aattcaaagg gagttggtaa acgctgggtga gtctattcc  
241 actttgctaa gggaataacc actaagggtta attgactaga ctgtatttta gaatgcctt  
301 tggacaggat aaagaactta agtcattgca tattcaatc t

**D28913      Exon 7**

1 gatctttcca aatctgaaat tgttccatag gttgcctatt acataattga tagttaata  
61 acttgaaaat actgatgctc tctaaaatga tttaaaaaat tctgtttggc ataggtgtgg  
121 tacatgtggc ttgtctact catgtggata gcatggattt gattacaaaa ggtgacctta  
181 tagaaataga gagatgtgag cctgtgaggt ccaaggtaat gaatgatgcc ctctgtaaac  
241 acattttctg gggatgttta ctacaatcac atactagtgt gtataaaa

**Figure 24. (Page 46 of 46)****D28914      Exon 8**

1 ttttttcca atggaaatta ttgcaagttc ctacatcttg atattgcttt cataatttat  
61 actaacataa aataatattt ttactgttt tgcaatgtct tttaatttc tgtattgcag  
121 ctagaggaag tccaaagaaa acttggattt gctctttctg acatctcggg ggtagcaat  
181 tattctctcg agtgggagct ggaccctgta aaggatgttc taattcttc tgctctgaga  
241 cgaatgctat gggctgcaga tgacttctta gaggatttgc cttttgagca aataggtaga  
301 tggtttggg gtgtggaagc ttggaagcgg tcaggtagtt ggctactttc tgcttgatc  
361 tattaaatac tg

**D28915      Exon 9**

1 cctctgggtg cctttcctga gataatccac taagaatatt ttgtgttct tttctcaggg  
61 aatctaaggg aggaaattat caactgtgca caaggaaaaa aatagatatg tgaaagggtc  
121 acgtaaattt cctcacatca cagaagatta aaattcagaa aggagaaaac acagaccaa  
181 gagaagtatc taagaccaa gggatgtgtt ttattaatgt ctaggatgaa gaaatgcata  
241 gaacattgta gtacttgtaa ataactagaa ataacatgat ttatgcataa ttgtgaaaaa  
301 taataataat tttcttggga ttatgttct gtatctgtga aaaaataaat ttcttataaa  
361 actcgggtct aacttgagag tgtgtgtgat ttggaaaaa ttatgatttg tcagcatctt  
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481 ttt

Figure 25.

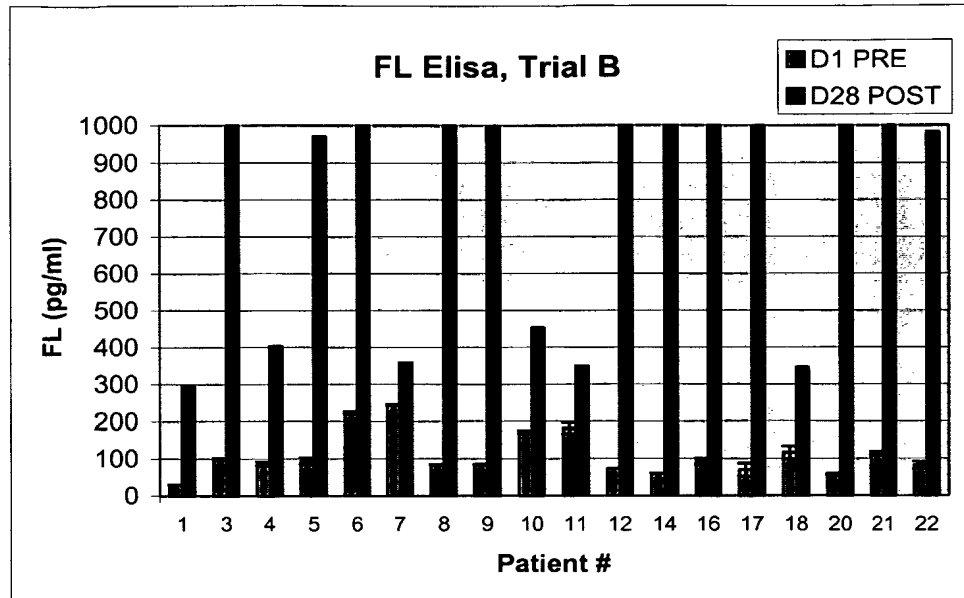


Figure 26.

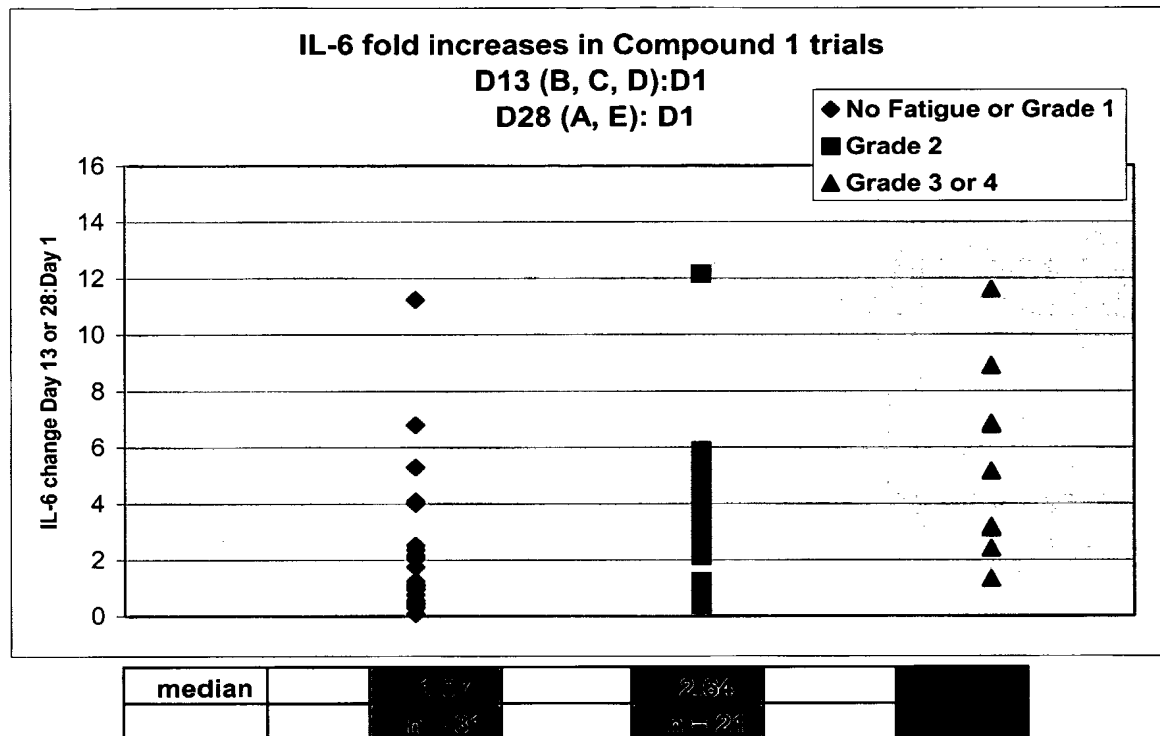


Figure 27.

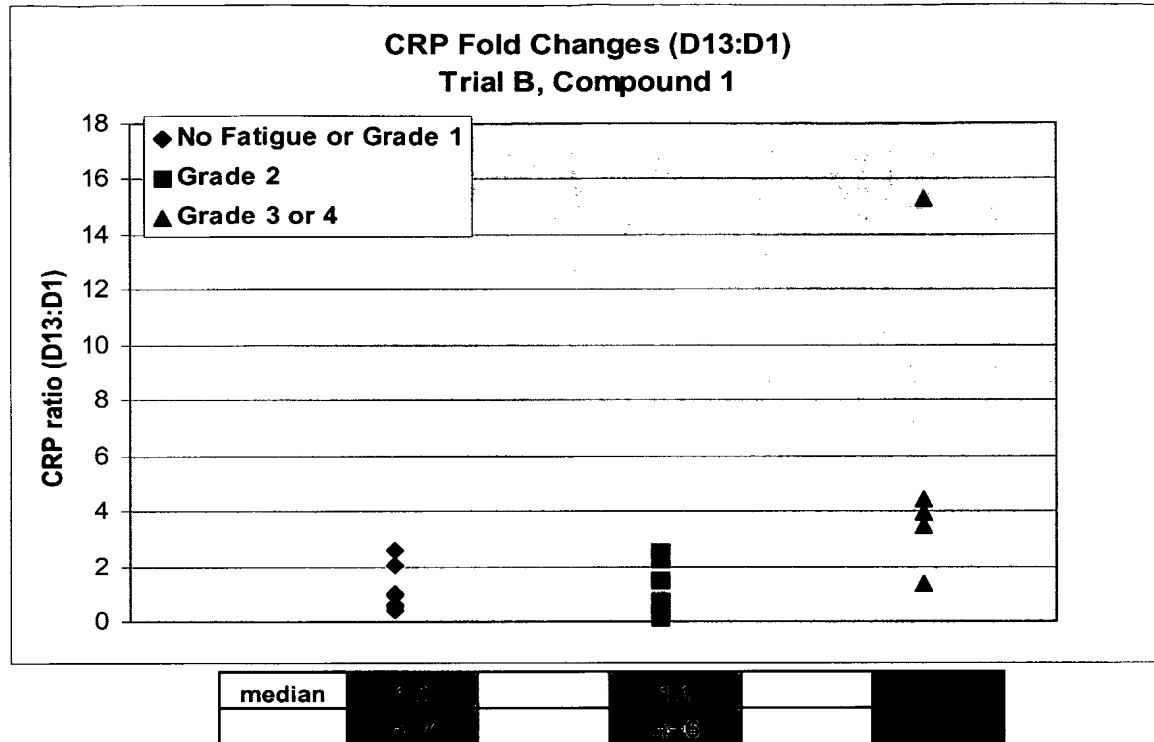
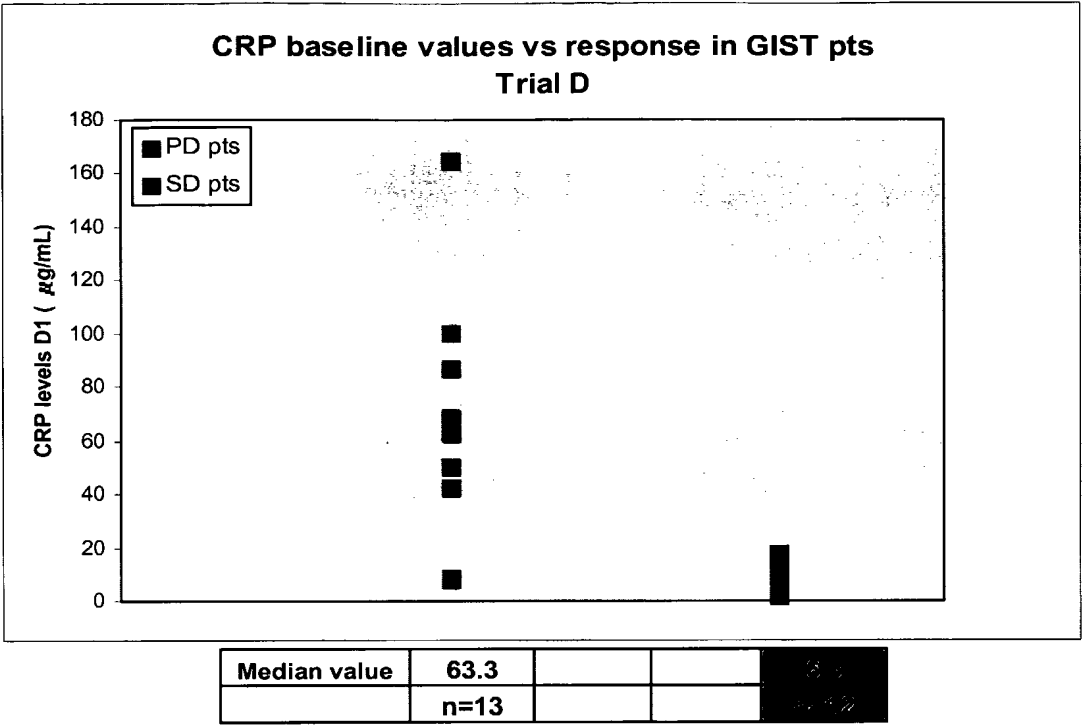


Figure 28.





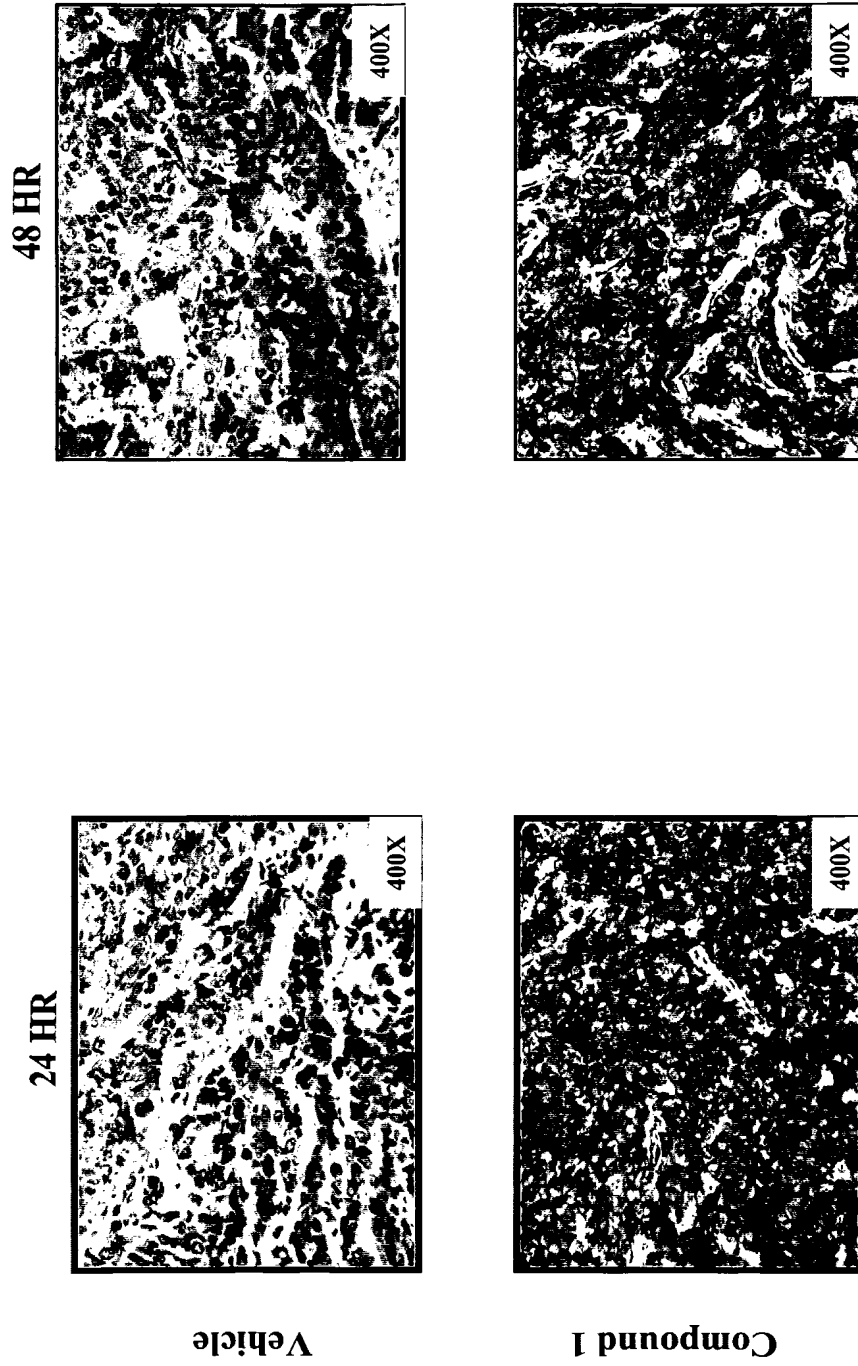


Figure 29.

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## SEQUENCE LISTING

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<120> NOVEL BIOMARKERS OF TYROSINE KINASE INHIBITOR EXPOSURE  
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&lt;130&gt; 038602/1593

&lt;140&gt;

&lt;141&gt;

&lt;150&gt; 60/380,872

&lt;151&gt; 2002-05-17

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&lt;151&gt; 2003-02-24

&lt;160&gt; 185

&lt;170&gt; PatentIn Ver. 2.1

&lt;210&gt; 1

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<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 4  
cctagtcctc agggcactgc 20

<210> 5  
<211> 21  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 5  
cccagaagtg gttgtttccc t 21

<210> 6  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 6  
gtccatgttt ttccttgagc ct 22

<210> 7  
<211> 19  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 7  
ctggaagcct gtgaattcc 19

<210> 8  
<211> 21  
<212> DNA  
<213> Artificial Sequence

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&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 8

gaatggctga ggctttcttg g

21

&lt;210&gt; 9

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 9

gctgacttcg gaactaaagg agaa

24

&lt;210&gt; 10

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 10

tgggacaggg aagacgatgt

20

&lt;210&gt; 11

&lt;211&gt; 23

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 11

ctgcctcgac acacataaac ctt

23

&lt;210&gt; 12

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 12

catctaagca tcagtgtgtg acca

24

&lt;210&gt; 13

&lt;211&gt; 22

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&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 13

atgatgagtc ggtcctcttt cc

22

&lt;210&gt; 14

&lt;211&gt; 28

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 14

tgacaattga aagtttaaaa ccatcata

28

&lt;210&gt; 15

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: PrOBE

&lt;400&gt; 15

tccattgtct tatgatccac

20

&lt;210&gt; 16

&lt;211&gt; 28

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 16

agttagaagt tagggtttag gcatcatt

28

&lt;210&gt; 17

&lt;211&gt; 21

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 17

taccatgcc ctcaactcaat c

21

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<210> 18  
<211> 18  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Probe

<400> 18  
aagtgtcagc attctcaa 18

<210> 19  
<211> 23  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 19  
ccagtgttgt gaggatgcat atc 23

<210> 20  
<211> 21  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 20  
cagtcaacat cagcgcaaag a 21

<210> 21  
<211> 17  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Probe

<400> 21  
attcccatgc cgtcgta 17

<210> 22  
<211> 32  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 22  
caaacctact gtatctctaa tacagtgtga ct 32

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<210> 23  
<211> 27  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 23  
gacagagatg attatccctt taaacca 27

<210> 24  
<211> 14  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Probe

<400> 24  
agcgctcacc tttg 14

<210> 25  
<211> 30  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 25  
cctacagaca gacatacata gacatttcaa 30

<210> 26  
<211> 25  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 26  
attatgcttc atgtttcctg gctta 25

<210> 27  
<211> 27  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Probe

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<400> 27  
ccaaattaag aaatattata ctaatca 27

<210> 28  
<211> 26  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 28  
gacaacagtt ctgagctgta atttcg 26

<210> 29  
<211> 25  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 29  
tgggtttaag ctggctgaat attat 25

<210> 30  
<211> 20  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Probe

<400> 30  
actctggaca ctctatatgt 20

<210> 31  
<211> 23  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 31  
tcagccagct taaaccata caa 23

<210> 32  
<211> 29  
<212> DNA  
<213> Artificial Sequence



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&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 32

tggcacgtat tagtttaaga tgaaagtag

29

&lt;210&gt; 33

&lt;211&gt; 18

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Probe

&lt;400&gt; 33

cttggtactg ctgattct

18

&lt;210&gt; 34

&lt;211&gt; 19

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 34

ttcagaggcc ccaccaatt

19

&lt;210&gt; 35

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 35

cccacatgag cttccacaca

20

&lt;210&gt; 36

&lt;211&gt; 15

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Probe

&lt;400&gt; 36

tctcggacac ttctc

15

&lt;210&gt; 37

&lt;211&gt; 22

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&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 37

tgaggcaggg acaagtcttt ct

22

&lt;210&gt; 38

&lt;211&gt; 21

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 38

accctgactg aaggctcatg a

21

&lt;210&gt; 39

&lt;211&gt; 19

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Probe

&lt;400&gt; 39

ctctttgaga cccagtg

19

&lt;210&gt; 40

&lt;211&gt; 26

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 40

tctaccgtcc ttgtcataac tttgtg

26

&lt;210&gt; 41

&lt;211&gt; 19

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: Primer

&lt;400&gt; 41

atgatgatgg gccctgtt

19

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<210> 42  
 <211> 15  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: Probe

<400> 42  
 cctttgccca agttg 15

<210> 43  
 <211> 22  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: Primer

<400> 43  
 tggacgtttt gtgatcgaag ag 22

<210> 44  
 <211> 26  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: Primer

<400> 44  
 aagtcaaggc ttctgtcttt tcttct 26

<210> 45  
 <211> 20  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: Probe

<400> 45  
 cttgagaatc ctttccaacc 20

<210> 46  
 <211> 10  
 <212> PRT  
 <213> Homo sapiens

<400> 46  
 Asp Ile Tyr Ser Ser Phe Gly Phe Pro Arg  
 1 5 10

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<210> 47  
 <211> 11  
 <212> PRT  
 <213> Homo sapiens

<400> 47  
 Asp Gly Phe Phe Tyr Phe Phe His Gly Thr Arg  
       1                  5                  10

<210> 48  
 <211> 114  
 <212> PRT  
 <213> Homo sapiens

<400> 48  
 Met Ser Leu Leu Ser Ser Arg Ala Ala Arg Val Pro Gly Pro Ser Ser  
       1                  5                  10                  15  
 Ser Leu Cys Ala Leu Leu Val Leu Leu Leu Leu Thr Gln Pro Gly  
                   20                  25                  30  
 Pro Ile Ala Ser Ala Gly Pro Ala Ala Ala Val Leu Arg Glu Leu Arg  
           35                  40                  45  
 Cys Val Cys Leu Gln Thr Thr Gln Gly Val His Pro Lys Met Ile Ser  
       50                  55                  60  
 Asn Leu Gln Val Phe Ala Ile Gly Pro Gln Cys Ser Lys Val Glu Val  
       65                  70                  75                  80  
 Val Ala Ser Leu Lys Asn Gly Lys Glu Ile Cys Leu Asp Pro Glu Ala  
                   85                  90                  95  
 Pro Phe Leu Lys Lys Val Ile Gln Lys Ile Leu Asp Gly Gly Asn Lys  
           100                  105                  110  
 Glu Asn

<210> 49  
 <211> 120  
 <212> PRT  
 <213> Homo sapiens

<400> 49  
 Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala  
       1                  5                  10                  15  
 Leu Gly Ser Gln Ala Arg Val Thr Lys Asp Ala Glu Thr Glu Phe Met  
           20                  25                  30  
 Met Ser Lys Leu Pro Leu Glu Asn Pro Val Leu Leu Asp Arg Phe His  
       35                  40                  45  
 Ala Thr Ser Ala Asp Cys Cys Ile Ser Tyr Thr Pro Arg Ser Ile Pro  
       50                  55                  60

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Cys Ser Leu Leu Glu Ser Tyr Phe Glu Thr Asn Ser Glu Cys Ser Lys  
 65 70 75 80  
 Pro Gly Val Ile Phe Leu Thr Lys Lys Gly Arg Arg Phe Cys Ala Asn  
 85 90 95  
 Pro Ser Asp Lys Gln Val Gln Val Cys Met Arg Met Leu Lys Leu Asp  
 100 105 110  
 Thr Arg Ile Lys Thr Arg Lys Asn  
 115 120

<210> 50  
 <211> 902  
 <212> PRT  
 <213> Homo sapiens

<400> 50  
 Met Ser Glu Phe Arg Ile His His Asp Val Asn Glu Leu Leu Ser Leu  
 1 5 10 15  
 Leu Arg Val His Gly Gly Asp Gly Ala Glu Val Tyr Ile Asp Leu Leu  
 20 25 30  
 Gln Lys Asn Arg Thr Pro Tyr Val Thr Thr Thr Val Ser Ala His Ser  
 35 40 45  
 Ala Lys Val Lys Ile Ala Glu Phe Ser Arg Thr Pro Glu Asp Phe Leu  
 50 55 60  
 Lys Lys Tyr Asp Glu Leu Lys Ser Lys Asn Thr Arg Asn Leu Asp Pro  
 65 70 75 80  
 Leu Val Tyr Leu Leu Ser Lys Leu Thr Glu Asp Lys Glu Thr Leu Gln  
 85 90 95  
 Tyr Leu Gln Gln Asn Ala Lys Glu Arg Ala Glu Leu Ala Ala Ala Ala  
 100 105 110  
 Val Gly Ser Ser Thr Thr Ser Ile Asn Val Pro Ala Ala Ala Ser Lys  
 115 120 125  
 Ile Ser Met Gln Glu Leu Glu Glu Leu Arg Lys Gln Leu Gly Ser Val  
 130 135 140  
 Ala Thr Gly Ser Thr Leu Gln Gln Ser Leu Glu Leu Lys Arg Lys Met  
 145 150 155 160  
 Leu Arg Asp Lys Gln Asn Lys Lys Asn Ser Gly Gln His Leu Pro Ile  
 165 170 175  
 Phe Pro Ala Trp Val Tyr Glu Arg Pro Ala Leu Ile Gly Asp Phe Leu  
 180 185 190  
 Ile Gly Ala Gly Ile Ser Thr Asp Thr Ala Leu Pro Ile Gly Thr Leu  
 195 200 205

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Leu | Ala | Ser | Gln | Glu | Ser | Ala | Val | Val | Glu | Asp | Leu | Leu | Tyr | Val | 210 | 215 | 220 |
| Leu | Val | Gly | Val | Asp | Gly | Arg | Tyr | Val | Ser | Ala | Gln | Pro | Leu | Ala | Gly | 225 | 230 | 235 |
| Arg | Gln | Ser | Arg | Thr | Phe | Leu | Val | Asp | Pro | Asn | Leu | Asp | Leu | Ser | Ile | 245 | 250 | 255 |
| Arg | Glu | Leu | Val | His | Arg | Ile | Leu | Pro | Val | Ala | Ala | Ser | Tyr | Ser | Ala | 260 | 265 | 270 |
| Val | Thr | Arg | Phe | Ile | Glu | Glu | Lys | Ser | Ser | Phe | Glu | Tyr | Gly | Gln | Val | 275 | 280 | 285 |
| Asn | His | Ala | Leu | Ala | Ala | Ala | Met | Arg | Thr | Leu | Val | Lys | Glu | His | Leu | 290 | 295 | 300 |
| Ile | Leu | Val | Ser | Gln | Leu | Glu | Gln | Leu | His | Arg | Gln | Gly | Leu | Leu | Ser | 305 | 310 | 315 |
| Leu | Gln | Lys | Leu | Trp | Phe | Tyr | Ile | Gln | Pro | Ala | Met | Arg | Thr | Met | Asp | 325 | 330 | 335 |
| Ile | Leu | Ala | Ser | Leu | Ala | Thr | Ser | Val | Asp | Lys | Gly | Glu | Cys | Leu | Gly | 340 | 345 | 350 |
| Gly | Ser | Thr | Leu | Ser | Leu | Leu | His | Asp | Arg | Ser | Phe | Ser | Tyr | Thr | Gly | 355 | 360 | 365 |
| Asp | Ser | Gln | Ala | Gln | Glu | Leu | Cys | Leu | Tyr | Leu | Thr | Lys | Ala | Ala | Ser | 370 | 375 | 380 |
| Ala | Pro | Tyr | Phe | Glu | Val | Leu | Glu | Lys | Trp | Ile | Tyr | Arg | Gly | Ile | Ile | 385 | 390 | 395 |
| His | Asp | Pro | Tyr | Ser | Glu | Phe | Met | Val | Glu | Glu | His | Glu | Leu | Arg | Lys | 405 | 410 | 415 |
| Glu | Arg | Ile | Gln | Glu | Asp | Tyr | Asn | Asp | Lys | Tyr | Trp | Asp | Gln | Arg | Tyr | 420 | 425 | 430 |
| Thr | Ile | Val | Gln | Gln | Gln | Ile | Pro | Ser | Phe | Leu | Gln | Lys | Met | Ala | Asp | 435 | 440 | 445 |
| Lys | Ile | Leu | Ser | Thr | Gly | Lys | Tyr | Leu | Asn | Val | Val | Arg | Glu | Cys | Gly | 450 | 455 | 460 |
| His | Asp | Val | Thr | Cys | Pro | Val | Ala | Lys | Glu | Ile | Ile | Tyr | Thr | Leu | Lys | 465 | 470 | 475 |
| Glu | Arg | Ala | Tyr | Val | Glu | Gln | Ile | Glu | Lys | Ala | Phe | Asn | Tyr | Ala | Ser | 485 | 490 | 495 |
| Lys | Val | Leu | Leu | Asp | Phe | Leu | Met | Glu | Glu | Lys | Glu | Leu | Val | Ala | His | 500 | 505 | 510 |

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Leu Arg Ser Ile Lys Arg Tyr Phe Leu Met Asp Gln Gly Asp Phe Phe  
 515 520 525  
 Val His Phe Met Asp Leu Ala Glu Glu Glu Leu Arg Lys Pro Val Glu  
 530 535 540  
 Asp Ile Thr Pro Pro Arg Leu Glu Ala Leu Leu Glu Leu Ala Leu Arg  
 545 550 555 560  
 Met Ser Thr Ala Asn Thr Asp Pro Phe Lys Asp Asp Leu Lys Ile Asp  
 565 570 575  
 Leu Met Pro His Asp Leu Ile Thr Gln Leu Leu Arg Val Leu Ala Ile  
 580 585 590  
 Glu Thr Lys Gln Glu Lys Ala Met Ala His Ala Asp Pro Thr Glu Leu  
 595 600 605  
 Ala Leu Ser Gly Leu Glu Ala Phe Ser Phe Asp Tyr Ile Val Lys Trp  
 610 615 620  
 Pro Leu Ser Leu Ile Ile Asn Arg Lys Ala Leu Thr Arg Tyr Gln Met  
 625 630 635 640  
 Leu Phe Arg His Met Phe Tyr Cys Lys His Val Glu Arg Gln Leu Cys  
 645 650 655  
 Ser Val Trp Ile Ser Asn Lys Thr Ala Lys Gln His Ser Leu His Ser  
 660 665 670  
 Ala Gln Trp Phe Ala Gly Ala Phe Thr Leu Arg Gln Arg Met Leu Asn  
 675 680 685  
 Phe Val Gln Asn Ile Gln Tyr Tyr Met Met Phe Glu Val Met Glu Pro  
 690 695 700  
 Thr Trp His Ile Leu Glu Lys Asn Leu Lys Ser Ala Ser Asn Ile Asp  
 705 710 715 720  
 Asp Val Leu Gly His His Thr Gly Phe Leu Asp Thr Cys Leu Lys Asp  
 725 730 735  
 Cys Met Leu Thr Asn Pro Glu Leu Leu Lys Val Phe Ser Lys Leu Met  
 740 745 750  
 Ser Val Cys Val Met Phe Thr Asn Cys Met Gln Lys Phe Thr Gln Ser  
 755 760 765  
 Met Lys Leu Asp Gly Glu Leu Gly Gly Gln Thr Leu Glu His Ser Thr  
 770 775 780  
 Val Leu Gly Leu Pro Ala Gly Ala Glu Glu Arg Ala Arg Lys Glu Leu  
 785 790 795 800  
 Ala Arg Lys His Leu Ala Glu His Ala Asp Thr Val Gln Leu Val Ser  
 805 810 815

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Gly Phe Glu Ala Thr Ile Asn Lys Phe Asp Lys Asn Phe Ser Ala His  
                     820                    825                    830  
 Leu Leu Asp Leu Leu Ala Arg Leu Ser Ile Tyr Ser Thr Ser Asp Cys  
                     835                    840                    845  
 Glu His Gly Met Ala Ser Val Ile Ser Arg Leu Asp Phe Asn Gly Phe  
                     850                    855                    860  
 Tyr Thr Glu Arg Leu Glu Arg Leu Ser Ala Glu Arg Ser Gln Lys Ala  
                     865                    870                    875                    880  
 Thr Pro Gln Val Pro Val Leu Arg Gly Pro Pro Ala Pro Ala Pro Arg  
                     885                    890                    895  
 Val Ala Val Thr Ala Gln  
                     900

<210> 51  
 <211> 252  
 <212> PRT  
 <213> Homo sapiens

<400> 51  
 Met Arg Ala Pro Leu Leu Pro Pro Ala Pro Val Val Leu Ser Leu Leu  
   1                    5                    10                    15  
 Ile Leu Gly Ser Gly His Tyr Ala Ala Gly Leu Asp Leu Asn Asp Thr  
                     20                    25                    30  
 Tyr Ser Gly Lys Arg Glu Pro Phe Ser Gly Asp His Ser Ala Asp Gly  
                     35                    40                    45  
 Phe Glu Val Thr Ser Arg Ser Glu Met Ser Ser Gly Ser Glu Ile Ser  
                     50                    55                    60  
 Pro Val Ser Glu Met Pro Ser Ser Ser Glu Pro Ser Ser Gly Ala Asp  
                     65                    70                    75                    80  
 Tyr Asp Tyr Ser Glu Glu Tyr Asp Asn Glu Pro Gln Ile Pro Gly Tyr  
                     85                    90                    95  
 Ile Val Asp Asp Ser Val Arg Val Glu Gln Val Val Lys Pro Pro Gln  
                     100                    105                    110  
 Asn Lys Thr Glu Ser Glu Asn Thr Ser Asp Lys Pro Lys Arg Lys Lys  
                     115                    120                    125  
 Lys Gly Gly Lys Asn Gly Lys Asn Arg Arg Asn Arg Lys Lys Lys Asn  
                     130                    135                    140  
 Pro Cys Asn Ala Glu Phe Gln Asn Phe Cys Ile His Gly Glu Cys Lys  
                     145                    150                    155                    160  
 Tyr Ile Glu His Leu Glu Ala Val Thr Cys Lys Cys Gln Gln Glu Tyr  
                     165                    170                    175



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Phe Gly Glu Arg Cys Gly Glu Lys Ser Met Lys Thr His Ser Met Ile  
 180 185 190

Asp Ser Ser Leu Ser Lys Ile Ala Leu Ala Ala Ile Ala Ala Phe Met  
 195 200 205

Ser Ala Val Ile Leu Thr Ala Val Ala Val Ile Thr Val Gln Leu Arg  
 210 215 220

Arg Gln Tyr Val Arg Lys Tyr Glu Gly Glu Ala Glu Glu Arg Lys Lys  
 225 230 235 240

Leu Arg Gln Glu Asn Gly Asn Val His Ala Ile Ala  
 245 250

<210> 52  
 <211> 271  
 <212> PRT  
 <213> Homo sapiens

<400> 52  
 Met Ala Lys Val Pro Asp Met Phe Glu Asp Leu Lys Asn Cys Tyr Ser  
 1 5 10 15

Glu Asn Glu Glu Asp Ser Ser Ser Ile Asp His Leu Ser Leu Asn Gln  
 20 25 30

Lys Ser Phe Tyr His Val Ser Tyr Gly Pro Leu His Glu Gly Cys Met  
 35 40 45

Asp Gln Ser Val Ser Leu Ser Ile Ser Glu Thr Ser Lys Thr Ser Lys  
 50 55 60

Leu Thr Phe Lys Glu Ser Met Val Val Val Ala Thr Asn Gly Lys Val  
 65 70 75 80

Leu Lys Lys Arg Arg Leu Ser Leu Ser Gln Ser Ile Thr Asp Asp Asp  
 85 90 95

Leu Glu Ala Ile Ala Asn Asp Ser Glu Glu Glu Ile Ile Lys Pro Arg  
 100 105 110

Ser Ala Pro Phe Ser Phe Leu Ser Asn Val Lys Tyr Asn Phe Met Arg  
 115 120 125

Ile Ile Lys Tyr Glu Phe Ile Leu Asn Asp Ala Leu Asn Gln Ser Ile  
 130 135 140

Ile Arg Ala Asn Asp Gln Tyr Leu Thr Ala Ala Ala Leu His Asn Leu  
 145 150 155 160

Asp Glu Ala Val Lys Phe Asp Met Gly Ala Tyr Lys Ser Ser Lys Asp  
 165 170 175

Asp Ala Lys Ile Thr Val Ile Leu Arg Ile Ser Lys Thr Gln Leu Tyr  
 180 185 190

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Val Thr Ala Gln Asp Glu Asp Gln Pro Val Leu Leu Lys Glu Met Pro  
 195 200 205

Glu Ile Pro Lys Thr Ile Thr Gly Ser Glu Thr Asn Leu Leu Phe Phe  
 210 215 220

Trp Glu Thr His Gly Thr Lys Asn Tyr Phe Thr Ser Val Ala His Pro  
 225 230 235 240

Asn Leu Phe Ile Ala Thr Lys Gln Asp Tyr Trp Val Cys Leu Ala Gly  
 245 250 255

Gly Pro Pro Ser Ile Thr Asp Phe Gln Ile Leu Glu Asn Gln Ala  
 260 265 270

<210> 53  
 <211> 269  
 <212> PRT  
 <213> Homo sapiens

<400> 53  
 Met Ala Glu Val Pro Glu Leu Ala Ser Glu Met Met Ala Tyr Tyr Ser  
 1 5 10 15

Gly Asn Glu Asp Asp Leu Phe Phe Glu Ala Asp Gly Pro Lys Gln Met  
 20 25 30

Lys Cys Ser Phe Gln Asp Leu Asp Leu Cys Pro Leu Asp Gly Gly Ile  
 35 40 45

Gln Leu Arg Ile Ser Asp His His Tyr Ser Lys Gly Phe Arg Gln Ala  
 50 55 60

Ala Ser Val Val Val Ala Met Asp Lys Leu Arg Lys Met Leu Val Pro  
 65 70 75 80

Cys Pro Gln Thr Phe Gln Glu Asn Asp Leu Ser Thr Phe Phe Pro Phe  
 85 90 95

Ile Phe Glu Glu Glu Pro Ile Phe Phe Asp Thr Trp Asp Asn Glu Ala  
 100 105 110

Tyr Val His Asp Ala Pro Val Arg Ser Leu Asn Cys Thr Leu Arg Asp  
 115 120 125

Ser Gln Gln Lys Ser Leu Val Met Ser Gly Pro Tyr Glu Leu Lys Ala  
 130 135 140

Leu His Leu Gln Gly Gln Asp Met Glu Gln Gln Val Val Phe Ser Met  
 145 150 155 160

Ser Phe Val Gln Gly Glu Glu Ser Asn Asp Lys Ile Pro Val Ala Leu  
 165 170 175

Gly Leu Lys Glu Lys Asn Leu Tyr Leu Ser Cys Val Leu Lys Asp Asp  
 180 185 190

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Lys Pro Thr Leu Gln Leu Glu Ser Val Asp Pro Lys Asn Tyr Pro Lys  
           195                          200                          205  
 Lys Lys Met Glu Lys Arg Phe Val Phe Asn Lys Ile Glu Ile Asn Asn  
           210                          215                          220  
 Lys Leu Glu Phe Glu Ser Ala Gln Phe Pro Asn Trp Tyr Ile Ser Thr  
   225                          230                          235                          240  
 Ser Gln Ala Glu Asn Met Pro Val Phe Leu Gly Gly Thr Lys Gly Gly  
                           245                          250                          255  
 Gln Asp Ile Thr Asp Phe Thr Met Gln Phe Val Ser Ser  
                           260                          265

<210> 54  
 <211> 153  
 <212> PRT  
 <213> Homo sapiens

<400> 54  
 Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu  
   1                          5                          10                          15  
 Val Thr Asn Ser Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu  
                           20                          25                          30  
 Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile  
                           35                          40                          45  
 Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe  
                           50                          55                          60  
 Tyr Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu  
   65                          70                          75                          80  
 Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys  
                           85                          90                          95  
 Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile  
                           100                          105                          110  
 Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala  
                           115                          120                          125  
 Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe  
   130                          135                          140  
 Cys Gln Ser Ile Ile Ser Thr Leu Thr  
   145                          150

<210> 55  
 <211> 125  
 <212> PRT  
 <213> Homo sapiens

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&lt;400&gt; 55

Met Lys Lys Ser Gly Val Leu Phe Leu Leu Gly Ile Ile Leu Leu Val  
 1 5 10 15

Leu Ile Gly Val Gln Gly Thr Pro Val Val Arg Lys Gly Arg Cys Ser  
 20 25 30

Cys Ile Ser Thr Asn Gln Gly Thr Ile His Leu Gln Ser Leu Lys Asp  
 35 40 45

Leu Lys Gln Phe Ala Pro Ser Pro Ser Cys Glu Lys Ile Glu Ile Ile  
 50 55 60

Ala Thr Leu Lys Asn Gly Val Gln Thr Cys Leu Asn Pro Asp Ser Ala  
 65 70 75 80

Asp Val Lys Glu Leu Ile Lys Lys Trp Glu Lys Gln Val Ser Gln Lys  
 85 90 95

Lys Lys Gln Lys Asn Gly Lys Lys His Gln Lys Lys Lys Val Leu Lys  
 100 105 110

Val Arg Lys Ser Gln Arg Ser Arg Gln Lys Lys Thr Thr  
 115 120 125

&lt;210&gt; 56

&lt;211&gt; 210

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 56

Met Leu Pro Leu Pro Ser Cys Ser Leu Pro Ile Leu Leu Leu Phe Leu  
 1 5 10 15

Leu Pro Ser Val Pro Ile Glu Ser Gln Pro Pro Pro Ser Thr Leu Pro  
 20 25 30

Pro Phe Leu Ala Pro Glu Trp Asp Leu Leu Ser Pro Arg Val Val Leu  
 35 40 45

Ser Arg Gly Ala Pro Ala Gly Pro Pro Leu Leu Phe Leu Leu Glu Ala  
 50 55 60

Gly Ala Phe Arg Glu Ser Ala Gly Ala Pro Ala Asn Arg Ser Arg Arg  
 65 70 75 80

Gly Val Ser Glu Thr Ala Pro Ala Ser Arg Arg Gly Glu Leu Ala Val  
 85 90 95

Cys Asp Ala Val Ser Gly Trp Val Thr Asp Arg Arg Thr Ala Val Asp  
 100 105 110

Leu Arg Gly Arg Glu Val Glu Val Leu Gly Glu Val Pro Ala Ala Gly  
 115 120 125

Gly Ser Pro Leu Arg Gln Tyr Phe Phe Glu Thr Arg Cys Lys Ala Asp  
 130 135 140

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Asn Ala Glu Glu Gly Gly Pro Gly Ala Gly Gly Gly Gly Cys Arg Gly  
 145 150 155 160  
 Val Asp Arg Arg His Trp Val Ser Glu Cys Lys Ala Lys Gln Ser Tyr  
 165 170 175  
 Val Arg Ala Leu Thr Ala Asp Ala Gln Gly Arg Val Gly Trp Arg Trp  
 180 185 190  
 Ile Arg Ile Asp Thr Ala Cys Val Cys Thr Leu Leu Ser Arg Thr Gly  
 195 200 205  
 Arg Ala  
 210

<210> 57  
 <211> 259  
 <212> PRT  
 <213> Homo sapiens

<400> 57  
 Met Ser Glu Val Pro Val Ala Arg Val Trp Leu Val Leu Leu Leu Leu  
 1 5 10 15  
 Thr Val Gln Val Gly Val Thr Ala Gly Ala Pro Trp Gln Cys Ala Pro  
 20 25 30  
 Cys Ser Ala Glu Lys Leu Ala Leu Cys Pro Pro Val Ser Ala Ser Cys  
 35 40 45  
 Ser Glu Val Thr Arg Ser Ala Gly Cys Gly Cys Cys Pro Met Cys Ala  
 50 55 60  
 Leu Pro Leu Gly Ala Ala Cys Gly Val Ala Thr Ala Arg Cys Ala Arg  
 65 70 75 80  
 Gly Leu Ser Cys Arg Ala Leu Pro Gly Glu Gln Gln Pro Leu His Ala  
 85 90 95  
 Leu Thr Arg Gly Gln Gly Ala Cys Val Gln Glu Ser Asp Ala Ser Ala  
 100 105 110  
 Pro His Ala Ala Glu Ala Gly Ser Pro Glu Ser Pro Glu Ser Thr Glu  
 115 120 125  
 Ile Thr Glu Glu Glu Leu Leu Asp Asn Phe His Leu Met Ala Pro Ser  
 130 135 140  
 Glu Glu Asp His Ser Ile Leu Trp Asp Ala Ile Ser Thr Tyr Asp Gly  
 145 150 155 160  
 Ser Lys Ala Leu His Val Thr Asn Ile Lys Lys Trp Lys Glu Pro Cys  
 165 170 175  
 Arg Ile Glu Leu Tyr Arg Val Val Glu Ser Leu Ala Lys Ala Gln Glu  
 180 185 190

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Thr Ser Gly Glu Glu Ile Ser Lys Phe Tyr Leu Pro Asn Cys Asn Lys  
           195                                  200                                  205  
 Asn Gly Phe Tyr His Ser Arg Gln Cys Glu Thr Ser Met Asp Gly Glu  
           210                                  215                                  220  
 Ala Gly Leu Cys Trp Cys Val Tyr Pro Trp Asn Gly Lys Arg Ile Pro  
   225                                  230                                  235                                  240  
 Gly Ser Pro Glu Ile Arg Gly Asp Pro Asn Cys Gln Ile Tyr Phe Asn  
                                   245                                  250                                  255  
 Val Gln Asn

<210> 58  
 <211> 107  
 <212> PRT  
 <213> Homo sapiens

<400> 58  
 Met Ala Arg Ala Thr Leu Ser Ala Ala Pro Ser Asn Pro Arg Leu Leu  
   1                                  5                                  10                                  15  
 Arg Val Ala Leu Leu Leu Leu Leu Val Ala Ala Ser Arg Arg Ala  
                                   20                                  25                                  30  
 Ala Gly Ala Pro Leu Ala Thr Glu Leu Arg Cys Gln Cys Leu Gln Thr  
                                   35                                  40                                  45  
 Leu Gln Gly Ile His Leu Lys Asn Ile Gln Ser Val Lys Val Lys Ser  
   50                                  55                                  60  
 Pro Gly Pro His Cys Ala Gln Thr Glu Val Ile Ala Thr Leu Lys Asn  
   65                                  70                                  75                                  80  
 Gly Gln Lys Ala Cys Leu Asn Pro Ala Ser Pro Met Val Lys Lys Ile  
                                   85                                  90                                  95  
 Ile Glu Lys Met Leu Lys Asn Gly Lys Ser Asn  
                                   100                                  105

<210> 59  
 <211> 455  
 <212> PRT  
 <213> Homo sapiens

<400> 59  
 Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu  
   1                                  5                                  10                                  15  
 Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro  
                                   20                                  25                                  30

|            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| His        | Leu        | Gly<br>35  | Asp        | Arg        | Glu        | Lys        | Arg<br>40  | Asp        | Ser        | Val        | Cys        | Pro<br>45  | Gln        | Gly        | Lys        |
| Tyr        | Ile<br>50  | His        | Pro        | Gln        | Asn        | Asn<br>55  | Ser        | Ile        | Cys        | Cys        | Thr<br>60  | Lys        | Cys        | His        | Lys        |
| Gly<br>65  | Thr        | Tyr        | Leu        | Tyr        | Asn<br>70  | Asp        | Cys        | Pro        | Gly        | Pro<br>75  | Gly        | Gln        | Asp        | Thr        | Asp<br>80  |
| Cys        | Arg        | Glu        | Cys        | Glu<br>85  | Ser        | Gly        | Ser        | Phe        | Thr<br>90  | Ala        | Ser        | Glu        | Asn        | His<br>95  | Leu        |
| Arg        | His        | Cys        | Leu<br>100 | Ser        | Cys        | Ser        | Lys        | Cys<br>105 | Arg        | Lys        | Glu        | Met        | Gly<br>110 | Gln        | Val        |
| Glu        | Ile        | Ser<br>115 | Ser        | Cys        | Thr        | Val        | Asp<br>120 | Arg        | Asp        | Thr        | Val        | Cys<br>125 | Gly        | Cys        | Arg        |
| Lys        | Asn<br>130 | Gln        | Tyr        | Arg        | His        | Tyr<br>135 | Trp        | Ser        | Glu        | Asn        | Leu<br>140 | Phe        | Gln        | Cys        | Phe        |
| Asn<br>145 | Cys        | Ser        | Leu        | Cys        | Leu<br>150 | Asn        | Gly        | Thr        | Val        | His<br>155 | Leu        | Ser        | Cys        | Gln        | Glu<br>160 |
| Lys        | Gln        | Asn        | Thr<br>165 | Val        | Cys        | Thr        | Cys        | His        | Ala<br>170 | Gly        | Phe        | Phe        | Leu        | Arg<br>175 | Glu        |
| Asn        | Glu        | Cys        | Val<br>180 | Ser        | Cys        | Ser        | Asn        | Cys<br>185 | Lys        | Lys        | Ser        | Leu        | Glu<br>190 | Cys        | Thr        |
| Lys        | Leu        | Cys<br>195 | Leu        | Pro        | Gln        | Ile        | Glu<br>200 | Asn        | Val        | Lys        | Gly        | Thr<br>205 | Glu        | Asp        | Ser        |
| Gly        | Thr<br>210 | Thr        | Val        | Leu        | Leu        | Pro<br>215 | Leu        | Val        | Ile        | Phe        | Phe<br>220 | Gly        | Leu        | Cys        | Leu        |
| Leu<br>225 | Ser        | Leu        | Leu        | Phe        | Ile<br>230 | Gly        | Leu        | Met        | Tyr        | Arg<br>235 | Tyr        | Gln        | Arg        | Trp        | Lys<br>240 |
| Ser        | Lys        | Leu        | Tyr        | Ser<br>245 | Ile        | Val        | Cys        | Gly        | Lys<br>250 | Ser        | Thr        | Pro        | Glu        | Lys<br>255 | Glu        |
| Gly        | Glu        | Leu        | Glu<br>260 | Gly        | Thr        | Thr        | Thr        | Lys<br>265 | Pro        | Leu        | Ala        | Pro        | Asn<br>270 | Pro        | Ser        |
| Phe        | Ser<br>275 | Pro        | Thr        | Pro        | Gly        | Phe        | Thr<br>280 | Pro        | Thr        | Leu        | Gly        | Phe<br>285 | Ser        | Pro        | Val        |
| Pro        | Ser<br>290 | Ser        | Thr        | Phe        | Thr        | Ser<br>295 | Ser        | Ser        | Thr        | Tyr        | Thr<br>300 | Pro        | Gly        | Asp        | Cys        |
| Pro<br>305 | Asn        | Phe        | Ala        | Ala        | Pro<br>310 | Arg        | Arg        | Glu        | Val        | Ala<br>315 | Pro        | Pro        | Tyr        | Gln        | Gly<br>320 |
| Ala        | Asp        | Pro        | Ile        | Leu<br>325 | Ala        | Thr        | Ala        | Leu        | Ala<br>330 | Ser        | Asp        | Pro        | Ile        | Pro<br>335 | Asn        |

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Pro Leu Gln Lys Trp Glu Asp Ser Ala His Lys Pro Gln Ser Leu Asp  
 340 345 350

Thr Asp Asp Pro Ala Thr Leu Tyr Ala Val Val Glu Asn Val Pro Pro  
 355 360 365

Leu Arg Trp Lys Glu Phe Val Arg Arg Leu Gly Leu Ser Asp His Glu  
 370 375 380

Ile Asp Arg Leu Glu Leu Gln Asn Gly Arg Cys Leu Arg Glu Ala Gln  
 385 390 395 400

Tyr Ser Met Leu Ala Thr Trp Arg Arg Arg Thr Pro Arg Arg Glu Ala  
 405 410 415

Thr Leu Glu Leu Leu Gly Arg Val Leu Arg Asp Met Asp Leu Leu Gly  
 420 425 430

Cys Leu Glu Asp Ile Glu Glu Ala Leu Cys Gly Pro Ala Ala Leu Pro  
 435 440 445

Pro Ala Pro Ser Leu Leu Arg  
 450 455

<210> 60  
 <211> 235  
 <212> PRT  
 <213> Homo sapiens

<400> 60  
 Met Thr Val Leu Ala Pro Ala Trp Ser Pro Thr Thr Tyr Leu Leu Leu  
 1 5 10 15

Leu Leu Leu Leu Ser Ser Gly Leu Ser Gly Thr Gln Asp Cys Ser Phe  
 20 25 30

Gln His Ser Pro Ile Ser Ser Asp Phe Ala Val Lys Ile Arg Glu Leu  
 35 40 45

Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val Thr Val Ala Ser Asn Leu  
 50 55 60

Gln Asp Glu Glu Leu Cys Gly Ala Leu Trp Arg Leu Val Leu Ala Gln  
 65 70 75 80

Arg Trp Met Glu Arg Leu Lys Thr Val Ala Gly Ser Lys Met Gln Gly  
 85 90 95

Leu Leu Glu Arg Val Asn Thr Glu Ile His Phe Val Thr Lys Cys Ala  
 100 105 110

Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe Val Gln Thr Asn Ile Ser  
 115 120 125

Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu Val Ala Leu Lys Pro Trp  
 130 135 140



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Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu Glu Leu Gln Cys Gln Pro  
 145 150 155 160

Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser Pro Arg Pro Leu Glu Ala  
 165 170 175

Thr Ala Pro Thr Ala Pro Gln Pro Pro Leu Leu Leu Leu Leu Leu  
 180 185 190

Pro Val Gly Leu Leu Leu Leu Ala Ala Ala Trp Cys Leu His Trp Gln  
 195 200 205

Arg Thr Arg Arg Arg Thr Pro Arg Pro Gly Glu Gln Val Pro Pro Val  
 210 215 220

Pro Ser Pro Gln Asp Leu Leu Leu Val Glu His  
 225 230 235

<210> 61  
 <211> 212  
 <212> PRT  
 <213> Homo sapiens

<400> 61  
 Met Asn Ser Phe Ser Thr Ser Ala Phe Gly Pro Val Ala Phe Ser Leu  
 1 5 10 15

Gly Leu Leu Leu Val Leu Pro Ala Ala Phe Pro Ala Pro Val Pro Pro  
 20 25 30

Gly Glu Asp Ser Lys Asp Val Ala Ala Pro His Arg Gln Pro Leu Thr  
 35 40 45

Ser Ser Glu Arg Ile Asp Lys Gln Ile Arg Tyr Ile Leu Asp Gly Ile  
 50 55 60

Ser Ala Leu Arg Lys Glu Thr Cys Asn Lys Ser Asn Met Cys Glu Ser  
 65 70 75 80

Ser Lys Glu Ala Leu Ala Glu Asn Asn Leu Asn Leu Pro Lys Met Ala  
 85 90 95

Glu Lys Asp Gly Cys Phe Gln Ser Gly Phe Asn Glu Glu Thr Cys Leu  
 100 105 110

Val Lys Ile Ile Thr Gly Leu Leu Glu Phe Glu Val Tyr Leu Glu Tyr  
 115 120 125

Leu Gln Asn Arg Phe Glu Ser Ser Glu Glu Gln Ala Arg Ala Val Gln  
 130 135 140

Met Ser Thr Lys Val Leu Ile Gln Phe Leu Gln Lys Lys Ala Lys Asn  
 145 150 155 160

Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr Thr Asn Ala Ser Leu Leu  
 165 170 175

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[illegible]

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<210> 62
<211> 99
<212> PRT
<213> Homo sapiens
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<400> 62
Met  Lys  Val  Ser  Ala  Ala  Leu  Leu  Cys  Leu  Leu  Leu  Ile  Ala  Ala  Thr
   1              5              10              15

Phe  Ile  Pro  Gln  Gly  Leu  Ala  Gln  Pro  Asp  Ala  Ile  Asn  Ala  Pro  Val
   20              25              30

Thr  Cys  Cys  Tyr  Asn  Phe  Thr  Asn  Arg  Lys  Ile  Ser  Val  Gln  Arg  Leu
   35              40              45

Ala  Ser  Tyr  Arg  Arg  Ile  Thr  Ser  Ser  Lys  Cys  Pro  Lys  Glu  Ala  Val
   50              55              60

Ile  Phe  Lys  Thr  Ile  Val  Ala  Lys  Glu  Ile  Cys  Ala  Asp  Pro  Lys  Gln
   65              70              75              80

Lys  Trp  Val  Gln  Asp  Ser  Met  Asp  His  Leu  Asp  Lys  Gln  Thr  Gln  Thr
   85              90              95

Pro  Lys  Thr

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<210> 63
<211> 233
<212> PRT
<213> Homo sapiens
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|          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| <400> 63 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Met      | Ser | Thr | Glu | Ser | Met | Ile | Arg | Asp | Val | Glu | Leu | Ala | Glu | Glu | Ala |
| 1        |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Leu      | Pro | Lys | Lys | Thr | Gly | Gly | Pro | Gln | Gly | Ser | Arg | Arg | Cys | Leu | Phe |
|          |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Leu      | Ser | Leu | Phe | Ser | Phe | Leu | Ile | Val | Ala | Gly | Ala | Thr | Thr | Leu | Phe |
|          |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Cys      | Leu | Leu | His | Phe | Gly | Val | Ile | Gly | Pro | Gln | Arg | Glu | Glu | Phe | Pro |
|          | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Arg      | Asp | Leu | Ser | Leu | Ile | Ser | Pro | Leu | Ala | Gln | Ala | Val | Arg | Ser | Ser |
| 65       |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|            |            |            |            |            |            |            |            |            |           |            |            |            |            |            |            |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|-----------|------------|------------|------------|------------|------------|------------|
| Ser        | Arg        | Thr        | Pro        | Ser<br>85  | Asp        | Lys        | Pro        | Val        | Ala<br>90 | His        | Val        | Val        | Ala        | Asn<br>95  | Pro        |
| Gln        | Ala        | Glu        | Gly<br>100 | Gln        | Leu        | Gln        | Trp        | Leu<br>105 | Asn       | Arg        | Arg        | Ala        | Asn<br>110 | Ala        | Leu        |
| Leu        | Ala        | Asn<br>115 | Gly        | Val        | Glu        | Leu        | Arg<br>120 | Asp        | Asn       | Gln        | Leu        | Val<br>125 | Val        | Pro        | Ser        |
| Glu        | Gly<br>130 | Leu        | Tyr        | Leu        | Ile        | Tyr<br>135 | Ser        | Gln        | Val       | Leu        | Phe<br>140 | Lys        | Gly        | Gln        | Gly        |
| Cys<br>145 | Pro        | Ser        | Thr        | His        | Val<br>150 | Leu        | Leu        | Thr        | His       | Thr<br>155 | Ile        | Ser        | Arg        | Ile        | Ala<br>160 |
| Val        | Ser        | Tyr        | Gln        | Thr<br>165 | Lys        | Val        | Asn        | Leu        | Leu       | Ser        | Ala        | Ile        | Lys        | Ser<br>175 | Pro        |
| Cys        | Gln        | Arg        | Glu<br>180 | Thr        | Pro        | Glu        | Gly        | Ala<br>185 | Glu       | Ala        | Lys        | Pro        | Trp<br>190 | Tyr        | Glu        |
| Pro        | Ile        | Tyr<br>195 | Leu        | Gly        | Gly        | Val        | Phe<br>200 | Gln        | Leu       | Glu        | Lys        | Gly<br>205 | Asp        | Arg        | Leu        |
| Ser        | Ala<br>210 | Glu        | Ile        | Asn        | Arg        | Pro<br>215 | Asp        | Tyr        | Leu       | Asp        | Phe<br>220 | Ala        | Glu        | Ser        | Gly        |
| Gln<br>225 | Val        | Tyr        | Phe        | Gly        | Ile<br>230 | Ile        | Ala        | Leu        |           |            |            |            |            |            |            |

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<400> 64
Met Ala Pro Leu Lys Met Leu Ala Leu Val Thr Leu Leu Leu Gly Ala
  1          5          10          15
Ser Leu Gln His Ile His Ala Ala Arg Gly Thr Asn Val Gly Arg Glu
          20          25          30
Cys Cys Leu Glu Tyr Phe Lys Gly Ala Ile Pro Leu Arg Lys Leu Lys
          35          40          45
Thr Trp Tyr Gln Thr Ser Glu Asp Cys Ser Arg Asp Ala Ile Val Phe
          50          55          60
Val Thr Val Gln Gly Arg Ala Ile Cys Ser Asp Pro Asn Asn Lys Arg
          65          70          75          80
Val Lys Asn Ala Val Lys Tyr Leu Gln Ser Leu Glu Arg Ser
          85          90

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&lt;210&gt; 65

&lt;211&gt; 267

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 65

Met Arg Leu Thr Val Leu Cys Ala Val Cys Leu Leu Pro Gly Ser Leu  
 1 5 10 15

Ala Leu Pro Leu Pro Gln Glu Ala Gly Gly Met Ser Glu Leu Gln Trp  
 20 25 30

Glu Gln Ala Gln Asp Tyr Leu Lys Arg Phe Tyr Leu Tyr Asp Ser Glu  
 35 40 45

Thr Lys Asn Ala Asn Ser Leu Glu Ala Lys Leu Lys Glu Met Gln Lys  
 50 55 60

Phe Phe Gly Leu Pro Ile Thr Gly Met Leu Asn Ser Arg Val Ile Glu  
 65 70 75 80

Ile Met Gln Lys Pro Arg Cys Gly Val Pro Asp Val Ala Glu Tyr Ser  
 85 90 95

Leu Phe Pro Asn Ser Pro Lys Trp Thr Ser Lys Val Val Thr Tyr Arg  
 100 105 110

Ile Val Ser Tyr Thr Arg Asp Leu Pro His Ile Thr Val Asp Arg Leu  
 115 120 125

Val Ser Lys Ala Leu Asn Met Trp Gly Lys Glu Ile Pro Leu His Phe  
 130 135 140

Arg Lys Val Val Trp Gly Thr Ala Asp Ile Met Ile Gly Phe Ala Arg  
 145 150 155 160

Gly Ala His Gly Asp Ser Tyr Pro Phe Asp Gly Pro Gly Asn Thr Leu  
 165 170 175

Ala His Ala Phe Ala Pro Gly Thr Gly Leu Gly Gly Asp Ala His Phe  
 180 185 190

Asp Glu Asp Glu Arg Trp Thr Asp Gly Ser Ser Leu Gly Ile Asn Phe  
 195 200 205

Leu Tyr Ala Ala Thr His Glu Leu Gly His Ser Leu Gly Met Gly His  
 210 215 220

Ser Ser Asp Pro Asn Ala Val Met Tyr Pro Thr Tyr Gly Asn Gly Asp  
 225 230 235 240

Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys  
 245 250 255

Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys  
 260 265

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&lt;210&gt; 66

&lt;211&gt; 707

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 66

Met Ser Leu Trp Gln Pro Leu Val Leu Val Leu Leu Val Leu Gly Cys  
 1 5 10 15

Cys Phe Ala Ala Pro Arg Gln Arg Gln Ser Thr Leu Val Leu Phe Pro  
 20 25 30

Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu Tyr  
 35 40 45

Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu Ser  
 50 55 60

Lys Ser Leu Gly Pro Ala Leu Leu Leu Leu Gln Lys Gln Leu Ser Leu  
 65 70 75 80

Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg Thr  
 85 90 95

Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu Gly  
 100 105 110

Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn Tyr  
 115 120 125

Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg Ala  
 130 135 140

Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val Tyr  
 145 150 155 160

Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His Gly  
 165 170 175

Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala Phe  
 180 185 190

Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp Glu  
 195 200 205

Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg Phe Gly Asn  
 210 215 220

Ala Asp Gly Ala Ala Cys His Phe Pro Phe Ile Phe Glu Gly Arg Ser  
 225 230 235 240

Tyr Ser Ala Cys Thr Thr Asp Gly Arg Ser Asp Gly Leu Pro Trp Cys  
 245 250 255

Ser Thr Thr Ala Asn Tyr Asp Thr Asp Asp Arg Phe Gly Phe Cys Pro  
 260 265 270

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Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly Lys Pro Cys  
 275 280 285  
 Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala Cys Thr Thr  
 290 295 300  
 Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn Tyr  
 305 310 315 320  
 Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser Thr  
 325 330 335  
 Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe Thr  
 340 345 350  
 Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly Asp  
 355 360 365  
 Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys Lys  
 370 375 380  
 Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala Ala  
 385 390 395 400  
 His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro Glu  
 405 410 415  
 Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His  
 420 425 430  
 Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro Glu  
 435 440 445  
 Pro Glu Pro Arg Pro Pro Thr Thr Thr Thr Pro Gln Pro Thr Ala Pro  
 450 455 460  
 Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu Arg  
 465 470 475 480  
 Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro  
 485 490 495  
 Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro Val  
 500 505 510  
 Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile Gly  
 515 520 525  
 Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu  
 530 535 540  
 Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp  
 545 550 555 560  
 Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Pro Leu Ser  
 565 570 575

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Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly  
                   580                                  585                                  590  
 Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly Ala  
                   595                                  600                                  605  
 Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys Met  
           610                                  615                                  620  
 Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala Gln  
   625                                  630                                  635                                  640  
 Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro Gly  
                   645                                  650                                  655  
 Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala Tyr  
                   660                                  665                                  670  
 Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu Leu  
                   675                                  680                                  685  
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<210> 67  
 <211> 167  
 <212> PRT  
 <213> Homo sapiens

<400> 67  
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                   20                                  25                                  30  
 Thr Leu Ile Lys Thr Ile Val Thr Arg Ile Asn Asp Ile Ser His Thr  
           35                                  40                                  45  
 Gln Ser Val Ser Ser Lys Gln Lys Val Thr Gly Leu Asp Phe Ile Pro  
           50                                  55                                  60  
 Gly Leu His Pro Ile Leu Thr Leu Ser Lys Met Asp Gln Thr Leu Ala  
   65                                  70                                  75                                  80  
 Val Tyr Gln Gln Ile Leu Thr Ser Met Pro Ser Arg Asn Val Ile Gln  
                   85                                  90                                  95  
 Ile Ser Asn Asp Leu Glu Asn Leu Arg Asp Leu Leu His Val Leu Ala  
                   100                                  105                                  110  
 Phe Ser Lys Ser Cys His Leu Pro Trp Ala Ser Gly Leu Glu Thr Leu  
           115                                  120                                  125

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Asp Ser Leu Gly Gly Val Leu Glu Ala Ser Gly Tyr Ser Thr Glu Val  
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Val Ala Leu Ser Arg Leu Gln Gly Ser Leu Gln Asp Met Leu Trp Gln  
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Leu Asp Leu Ser Pro Gly Cys  
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<210> 68  
 <211> 2619  
 <212> DNA  
 <213> Homo sapiens

<400> 68  
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<210> 69  
 <211> 711  
 <212> PRT  
 <213> Homo sapiens

<400> 69  
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 Gln Pro Glu Ala Thr Lys Cys Phe Gln Trp Gln Arg Asn Met Arg Lys  
 35 40 45  
 Val Arg Gly Pro Pro Val Ser Cys Ile Lys Arg Asp Ser Pro Ile Gln  
 50 55 60  
 Cys Ile Gln Ala Ile Ala Glu Asn Arg Ala Asp Ala Val Thr Leu Asp  
 65 70 75 80  
 Gly Gly Phe Ile Tyr Glu Ala Gly Leu Ala Pro Tyr Lys Leu Arg Pro  
 85 90 95  
 Val Ala Ala Glu Val Tyr Gly Thr Glu Arg Gln Pro Arg Thr His Tyr  
 100 105 110  
 Tyr Ala Val Ala Val Val Lys Lys Gly Gly Ser Phe Gln Leu Asn Glu  
 115 120 125  
 Leu Gln Gly Leu Lys Ser Cys His Thr Gly Leu Arg Arg Thr Ala Gly  
 130 135 140  
 Trp Asn Val Pro Thr Gly Thr Leu Arg Pro Phe Leu Asn Trp Thr Gly  
 145 150 155 160  
 Pro Pro Glu Pro Ile Glu Ala Ala Val Ala Arg Phe Phe Ser Ala Ser  
 165 170 175  
 Cys Val Pro Gly Ala Asp Lys Gly Gln Phe Pro Asn Leu Cys Arg Leu  
 180 185 190  
 Cys Ala Gly Thr Gly Glu Asn Lys Cys Ala Phe Ser Ser Gln Glu Pro  
 195 200 205  
 Tyr Phe Ser Tyr Ser Gly Ala Phe Lys Cys Leu Arg Asp Gly Ala Gly  
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 Asp Val Ala Phe Ile Arg Glu Ser Thr Val Phe Glu Asp Leu Ser Asp  
 225 230 235 240  
 Glu Ala Glu Arg Asp Glu Tyr Glu Leu Leu Cys Pro Asp Asn Thr Arg  
 245 250 255

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Lys Pro Val Asp Lys Phe Lys Asp Cys His Leu Ala Arg Val Pro Ser  
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 His Ala Val Val Ala Arg Ser Val Asn Gly Lys Glu Asp Ala Ile Trp  
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 Lys Phe Gln Leu Phe Gly Ser Pro Ser Gly Gln Lys Asp Leu Leu Phe  
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 Lys Asp Ser Ala Ile Gly Phe Ser Arg Val Pro Pro Arg Ile Asp Ser  
 325 330 335  
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 Lys Ser Glu Glu Glu Val Ala Ala Arg Arg Ala Arg Val Val Trp Cys  
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 420 425 430  
 Glu Asn Tyr Lys Ser Gln Gln Ser Ser Asp Pro Asp Pro Asn Cys Val  
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 450 455 460  
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 Thr Ala Val Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu  
 485 490 495  
 Phe Asn Gln Thr Gly Ser Cys Lys Phe Asp Glu Tyr Phe Ser Gln Ser  
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 Cys Ala Pro Gly Ser Asp Pro Arg Ser Asn Leu Cys Ala Leu Cys Ile  
 515 520 525  
 Gly Asp Glu Gln Gly Glu Asn Lys Cys Val Pro Asn Ser Asn Glu Arg  
 530 535 540  
 Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asn Ala Gly  
 545 550 555 560

|            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Asp        | Val        | Ala        | Phe        | Val<br>565 | Lys        | Asp        | Val        | Thr        | Val<br>570 | Leu        | Gln        | Asn        | Thr        | Asp<br>575 | Gly        |
| Asn        | Asn        | Asn        | Glu<br>580 | Ala        | Trp        | Ala        | Lys        | Asp<br>585 | Leu        | Lys        | Leu        | Ala        | Asp<br>590 | Phe        | Ala        |
| Leu        | Leu        | Cys<br>595 | Leu        | Asp        | Gly        | Lys        | Arg<br>600 | Lys        | Pro        | Val        | Thr        | Glu<br>605 | Ala        | Arg        | Ser        |
| Cys        | His<br>610 | Leu        | Ala        | Met        | Ala        | Pro<br>615 | Asn        | His        | Ala        | Val        | Val<br>620 | Ser        | Arg        | Met        | Asp        |
| Lys<br>625 | Val        | Glu        | Arg        | Leu        | Lys<br>630 | Gln        | Val        | Leu        | Leu        | His<br>635 | Gln        | Gln        | Ala        | Lys        | Phe<br>640 |
| Gly        | Arg        | Asn        | Gly        | Ser<br>645 | Asp        | Cys        | Pro        | Asp        | Lys<br>650 | Phe        | Cys        | Leu        | Phe        | Gln<br>655 | Ser        |
| Glu        | Thr        | Lys        | Asn<br>660 | Leu        | Leu        | Phe        | Asn        | Asp<br>665 | Asn        | Thr        | Glu        | Cys        | Leu<br>670 | Ala        | Arg        |
| Leu        | His        | Gly<br>675 | Lys        | Thr        | Thr        | Tyr        | Glu<br>680 | Lys        | Tyr        | Leu        | Gly        | Pro<br>685 | Gln        | Tyr        | Val        |
| Ala        | Gly<br>690 | Ile        | Thr        | Asn        | Leu        | Lys<br>695 | Lys        | Cys        | Ser        | Thr        | Ser<br>700 | Pro        | Leu        | Leu        | Glu        |
| Ala<br>705 | Cys        | Glu        | Phe        | Leu        | Arg<br>710 | Lys        |            |            |            |            |            |            |            |            |            |

| <400> 70   |             |             |            |             |             |     |  |
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| caggactcca | cctcagacct  | gatcccagcc  | ccacctctga | gcaagggtccc | tctgcagcag  | 120 |  |
| aacttccagg | acaaccaatt  | ccagggggaag | tggtatgtgg | taggcctggc  | agggaatgca  | 180 |  |
| attctcagag | aagacaaaga  | cccgcaaaaag | atgtatgcc  | ccatctatga  | gctgaaagaa  | 240 |  |
| gacaagagct | acaatgtcac  | ctccgtcctg  | tttaggaaaa | agaagtgtga  | ctactggatc  | 300 |  |
| aggacttttg | ttccagggtt  | ccagcccggc  | gagttcacgc | tgggcaacat  | taagagttac  | 360 |  |
| ctgtgattaa | cgagttacct  | cgtccgagtg  | gtgagcacca | actacaacca  | gcattgctatg | 420 |  |
| gtgttcttca | agaaagtttc  | tcaaaacagg  | gagtacttca | agatcacccct | ctacgggaga  | 480 |  |
| accaaggagc | tgacttcgga  | actaaaggag  | aacttcatcc | gcttctccaa  | atatctgggc  | 540 |  |
| ctccctgaaa | accacatcgt  | cttccctgtc  | ccaatcgacc | agtgtatcga  | cggctga     | 597 |  |

<400> 71  
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 Leu Ser Lys Val Pro Leu Gln Gln Asn Phe Gln Asp Asn Gln Phe Gln  
                     35                    40                    45  
 Gly Lys Trp Tyr Val Val Gly Leu Ala Gly Asn Ala Ile Leu Arg Glu  
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 Asp Lys Asp Pro Gln Lys Met Tyr Ala Thr Ile Tyr Glu Leu Lys Glu  
                     65                    70                    75                    80  
 Asp Lys Ser Tyr Asn Val Thr Ser Val Leu Phe Arg Lys Lys Lys Cys  
                     85                    90                    95  
 Asp Tyr Trp Ile Arg Thr Phe Val Pro Gly Cys Gln Pro Gly Glu Phe  
                     100                    105                    110  
 Thr Leu Gly Asn Ile Lys Ser Tyr Pro Gly Leu Thr Ser Tyr Leu Val  
                     115                    120                    125  
 Arg Val Val Ser Thr Asn Tyr Asn Gln His Ala Met Val Phe Phe Lys  
                     130                    135                    140  
 Lys Val Ser Gln Asn Arg Glu Tyr Phe Lys Ile Thr Leu Tyr Gly Arg  
                     145                    150                    155                    160  
 Thr Lys Glu Leu Thr Ser Glu Leu Lys Glu Asn Phe Ile Arg Phe Ser  
                     165                    170                    175  
 Lys Tyr Leu Gly Leu Pro Glu Asn His Ile Val Phe Pro Val Pro Ile  
                     180                    185                    190  
 Asp Gln Cys Ile Asp Gly  
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&lt;210&gt; 72

&lt;211&gt; 2334

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 72

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&lt;210&gt; 73

&lt;211&gt; 2116

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 73

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&lt;210&gt; 74

&lt;211&gt; 80

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 74

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          20             25             30
Thr Ser Ser Asn Ser Ser Gln Ser Thr Ser Asn Ser Gly Leu Ala Pro
          35             40             45
Asn Pro Thr Asn Ala Thr Thr Lys Ala Ala Gly Gly Ala Leu Gln Ser
          50             55             60
Thr Ala Ser Leu Phe Val Val Ser Leu Ser Leu Leu His Leu Tyr Ser
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&lt;210&gt; 75

&lt;211&gt; 1864

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 75

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gatgatatga atttaaagga gtctctcctt cgtggcatct atgcttacgg ttttgagaag 180
ccttccgcta ttcagcagag agctattatt ccctgtatta aagggtatga tgtgattgct 240
caagctcagt caggtactgg caagacagcc acatttgcta tttccatcct gcaacagttg 300
gagattgagt tcaaggagac ccaagcacta gtattggccc ccaccagaga actgggtcaa 360
cagatccaaa aggttaattct ggcacttggg gactatatgg gagccacttg tcatgcctgc 420
attggtggaa caaatgttcg aaatgaaatg caaaaactgc aggctgaagc accacatatt 480
gttggtggta caccggggag agtggttgat atgtttaaaca gaagatacct ttctccaaaa 540
tggatcaaaa tgtttgtttt ggatgaagca gatgaaatgt tgagccgtgg ttttaaggat 600
caaattctatg agattttcca aaaactaaac acaagtattc aggttggtgt tgcttctgcc 660
acaatgccaa ctgatgtgtt ggaagtgacc aaaaaattca tgagagatcc aattcgaatt 720
ctggtgaaaa aggaagaatt gacccttgaa ggaatcaaac agttttatat taatgttgag 780
agagaggaat ggaagttgga tacactttgt gacttgtagc agacactgac cattacacag 840
gctgttattt ttctcaatac gaggcgcaag gtggactggc tgactgagaa gatgcatgcc 900

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agagacttca cagtttctgc tctgcatggt gacatggacc agaaggagag agatgtttatc 960
atgaggggaat tccggtcagg gtcaagtcgt gttctgatca ctactgactt gttggctcgc 1020
gggattgatg tgcaacaagt gtctttgggt ataaattatg atctacctac caatcgtgaa 1080
aactatattc acagaattgg cagagggggt cgatttgga ggaaagggtg ggctataaac 1140
tttgttactg aagaagacaa gaggattcct cgtgacattg agactttcta caatactaca 1200
gtggaggaga tgcccatgaa tgtggctgac cttatttaat tcctgggatg agagttttgg 1260
atgcagtgct cgctgttgct gaataggcga tcacaacgtg cattgtgctt ctttctttgg 1320
gaatatttga atcttgtctc aatgctcata acggatcaga aatacagatt ttgatagcaa 1380
agcgacgtta gtcgtgagct cttgtgagga aagtcattgg ctttatcctc tttagagtta 1440
gactgttggg gtgggtataa aagatggggt ctgtaaaatc tttctttctt agaaatttat 1500
ttcctagttc tgtagaaatg gttgtattag atgttctcta tcatttaata atatacttgt 1560
ggactaaaag atataagtgc tgtataaaat cagccaatta tgttaaaacta gcatactctgc 1620
ctttattgtg tttgtcatta gcctgagtag aaaggccttt aaaatttttt tagaaagcat 1680
ttgaatgcat tttgtttggg attgtattta ttcaataaag tatttaatta gtgctaagt 1740
tgaactggac cctgttgcta agccccagca agcaatccta ggtagggttt aatccccagt 1800
aaaattgcc aattgacat gtcttaatga agtttgaatg ttaaataaat tgtatattca 1860
cttt

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&lt;210&gt; 76

&lt;211&gt; 407

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 76

```

Met Ser Gly Gly Ser Ala Asp Tyr Asn Arg Glu His Gly Gly Pro Glu
  1             5             10             15

Gly Met Asp Pro Asp Gly Val Ile Glu Ser Asn Trp Asn Glu Ile Val
             20             25             30

Asp Asn Phe Asp Asp Met Asn Leu Lys Glu Ser Leu Leu Arg Gly Ile
             35             40             45

Tyr Ala Tyr Gly Phe Glu Lys Pro Ser Ala Ile Gln Gln Arg Ala Ile
             50             55             60

Ile Pro Cys Ile Lys Gly Tyr Asp Val Ile Ala Gln Ala Gln Ser Gly
             65             70             75             80

Thr Gly Lys Thr Ala Thr Phe Ala Ile Ser Ile Leu Gln Gln Leu Glu
             85             90             95

Ile Glu Phe Lys Glu Thr Gln Ala Leu Val Leu Ala Pro Thr Arg Glu
             100            105            110

Leu Ala Gln Gln Ile Gln Lys Val Ile Leu Ala Leu Gly Asp Tyr Met
             115            120            125

Gly Ala Thr Cys His Ala Cys Ile Gly Gly Thr Asn Val Arg Asn Glu
             130            135            140

Met Gln Lys Leu Gln Ala Glu Ala Pro His Ile Val Val Gly Thr Pro
             145            150            155            160

Gly Arg Val Phe Asp Met Leu Asn Arg Arg Tyr Leu Ser Pro Lys Trp
             165            170            175

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Ile Lys Met Phe Val Leu Asp Glu Ala Asp Glu Met Leu Ser Arg Gly  
 180 185 190  
 Phe Lys Asp Gln Ile Tyr Glu Ile Phe Gln Lys Leu Asn Thr Ser Ile  
 195 200 205  
 Gln Val Val Phe Ala Ser Ala Thr Met Pro Thr Asp Val Leu Glu Val  
 210 215 220  
 Thr Lys Lys Phe Met Arg Asp Pro Ile Arg Ile Leu Val Lys Lys Glu  
 225 230 235 240  
 Glu Leu Thr Leu Glu Gly Ile Lys Gln Phe Tyr Ile Asn Val Glu Arg  
 245 250 255  
 Glu Glu Trp Lys Leu Asp Thr Leu Cys Asp Leu Tyr Glu Thr Leu Thr  
 260 265 270  
 Ile Thr Gln Ala Val Ile Phe Leu Asn Thr Arg Arg Lys Val Asp Trp  
 275 280 285  
 Leu Thr Glu Lys Met His Ala Arg Asp Phe Thr Val Ser Ala Leu His  
 290 295 300  
 Gly Asp Met Asp Gln Lys Glu Arg Asp Val Ile Met Arg Glu Phe Arg  
 305 310 315 320  
 Ser Gly Ser Ser Arg Val Leu Ile Thr Thr Asp Leu Leu Ala Arg Gly  
 325 330 335  
 Ile Asp Val Gln Gln Val Ser Leu Val Ile Asn Tyr Asp Leu Pro Thr  
 340 345 350  
 Asn Arg Glu Asn Tyr Ile His Arg Ile Gly Arg Gly Gly Arg Phe Gly  
 355 360 365  
 Arg Lys Gly Val Ala Ile Asn Phe Val Thr Glu Glu Asp Lys Arg Ile  
 370 375 380  
 Leu Arg Asp Ile Glu Thr Phe Tyr Asn Thr Thr Val Glu Glu Met Pro  
 385 390 395 400  
 Met Asn Val Ala Asp Leu Ile  
 405

&lt;210&gt; 77

&lt;211&gt; 1670

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 77

cggcagcagg caagtgcgc cgagggcctg agtgctccag tagccaccgc atctggagaa 60  
 ccagcgggta ccatggaggg gatcagtata tacacttcag ataactacac cgaggaaatg 120  
 ggctcagggg actatgactc catgaaggaa ccctgtttcc gtgaagaaaa tgctaatttc 180  
 aataaaatct tctgcccac catctactcc atcatcttct taactggcat tgtgggcaat 240  
 ggattgggtca tcttggtcat gggttaccag aagaaactga gaagcatgac ggacaagtac 300  
 aggctgcacc tgctcagtggc cgacctctc tttgtcatca cgcttccctt ctgggcagtt 360



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```

gatgccgtgg caaactggta ctttgggaac ttcttatgca aggcagtcca tgtcatctac 420
acagtcaacc tctacagcag tgtcctcatc ctggccttca tcagtctgga ccgctacctg 480
gccatcgctc acgccaccaa cagtcagagg ccaaggaagc tgttggctga aaaggtggtc 540
tatgttggcg tctggatccc tgccctcctg ctgactattc ccgacttcat ctttgccaac 600
gtcagtgagg cagatgacag atatatctgt gaccgcttct accccaatga cttgtgggtg 660
gttgtgttcc agtttcagca catcatgggt ggcccttatcc tgcctggtat tgtcatcctg 720
tcctgctatt gcattatcat ctccaagctg tcacactcca agggccacca gaagcgcaag 780
gccctcaaga ccacagtcac cctcatcctg gctttcttcg cctgttggct gccttactac 840
attgggatca gcatcgactc cttcatcctc ctggaaatca tcaagcaagg gtgtgagttt 900
gagaacactg tgcacaagtg gatttccatc accgaggccc tagctttctt ccactgttgt 960
ctgaacccca tcctctatgc tttccttgga gccaaattta aaacctctgc ccagcacgca 1020
ctcacctctg tgagcagagg gtccagcctc aagatcctct ccaaaggaaa gcgaggtgga 1080
cattcatctg tttccactga gtctgagttc tcaagttttc actccagcta acacagatgt 1140
aagagacttt tttttatacg ataaataact tttttttaag ttacacattt ttcagatata 1200
aaagactgac caatattgta cagtttttat tgcttggttg atttttgctc ttgtgtttct 1260
ttagtttttc gtgaaggttt aattgactta tttatataaa ttttttttgt ttcattattga 1320
tgtgtgtcta ggcaggacct gtggccaagt tcttagttgc tgtatgtctc gtggtaggac 1380
tgtagaaaag ggaactgaac attccagagc gtgtagtgaa tcacgtaaag ctagaaatga 1440
tccccagctg tttatgcata gataatctct ccattcccggt ggaacgtttt tcctgttctt 1500
aagacgtgat tttgctgtag aagatggcac ttataacca agcccaaagt ggtatagaaa 1560
tgctggtttt tcagttttca ggagtgggtt gatttcagca cctacagtgt acagtcctgt 1620
attaagttgt taataaaagt acatgttaaa cttaaaaaaa aaaaaaaaaa 1670

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&lt;210&gt; 78

&lt;211&gt; 352

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 78

```

Met Glu Gly Ile Ser Ile Tyr Thr Ser Asp Asn Tyr Thr Glu Glu Met
  1                      5                      10                      15

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```

Gly Ser Gly Asp Tyr Asp Ser Met Lys Glu Pro Cys Phe Arg Glu Glu
  .                20                25                30

```

```

Asn Ala Asn Phe Asn Lys Ile Phe Leu Pro Thr Ile Tyr Ser Ile Ile
  35                40                45

```

```

Phe Leu Thr Gly Ile Val Gly Asn Gly Leu Val Ile Leu Val Met Gly
  50                55                60

```

```

Tyr Gln Lys Lys Leu Arg Ser Met Thr Asp Lys Tyr Arg Leu His Leu
  65                70                75                80

```

```

Ser Val Ala Asp Leu Leu Phe Val Ile Thr Leu Pro Phe Trp Ala Val
  85                90                95

```

```

Asp Ala Val Ala Asn Trp Tyr Phe Gly Asn Phe Leu Cys Lys Ala Val
  100               105               110

```

```

His Val Ile Tyr Thr Val Asn Leu Tyr Ser Ser Val Leu Ile Leu Ala
  115               120               125

```

```

Phe Ile Ser Leu Asp Arg Tyr Leu Ala Ile Val His Ala Thr Asn Ser
  130               135               140

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Gln Arg Pro Arg Lys Leu Leu Ala Glu Lys Val Val Tyr Val Gly Val  
 145 150 155 160  
 Trp Ile Pro Ala Leu Leu Leu Thr Ile Pro Asp Phe Ile Phe Ala Asn  
 165 170 175  
 Val Ser Glu Ala Asp Asp Arg Tyr Ile Cys Asp Arg Phe Tyr Pro Asn  
 180 185 190  
 Asp Leu Trp Val Val Val Phe Gln Phe Gln His Ile Met Val Gly Leu  
 195 200 205  
 Ile Leu Pro Gly Ile Val Ile Leu Ser Cys Tyr Cys Ile Ile Ile Ser  
 210 215 220  
 Lys Leu Ser His Ser Lys Gly His Gln Lys Arg Lys Ala Leu Lys Thr  
 225 230 235 240  
 Thr Val Ile Leu Ile Leu Ala Phe Phe Ala Cys Trp Leu Pro Tyr Tyr  
 245 250 255  
 Ile Gly Ile Ser Ile Asp Ser Phe Ile Leu Leu Glu Ile Ile Lys Gln  
 260 265 270  
 Gly Cys Glu Phe Glu Asn Thr Val His Lys Trp Ile Ser Ile Thr Glu  
 275 280 285  
 Ala Leu Ala Phe Phe His Cys Cys Leu Asn Pro Ile Leu Tyr Ala Phe  
 290 295 300  
 Leu Gly Ala Lys Phe Lys Thr Ser Ala Gln His Ala Leu Thr Ser Val  
 305 310 315 320  
 Ser Arg Gly Ser Ser Leu Lys Ile Leu Ser Lys Gly Lys Arg Gly Gly  
 325 330 335  
 His Ser Ser Val Ser Thr Glu Ser Glu Ser Ser Ser Phe His Ser Ser  
 340 345 350

<210> 79  
 <211> 1262  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (53)..(53)  
 <223> n is a, c, g, or t

<220>  
 <221> misc\_feature  
 <222> (83)..(83)  
 <223> n is a, c, g, or t

<220>  
 <221> misc\_feature

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<222> (897)..(897)  
 <223> n is a, c, g, or t

<400> 79  
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 cagagccgct ggtagcctaa ggnggggggg cagccaggag aaagccccgc cgctgctcgt 120  
 cccgcccctc gggtgccagc accgcccctg ctgcggcggg tgagggggcg ggcggggccg 180  
 cggcgtatat aaggctaggc ggggcgcccgc tcttttgttt cttgctgcag caacgcgagt 240  
 gggagcacca ggatctcggg ctcggaacga gactgcacgg tgacgtgacg gccggggcgg 300  
 ggcccagggt gtggtcggat ccggtgcacc gcgggcgcgc aaccgggaca ggcgttctc 360  
 ggaccggagc cagggggccgc gaccacgccc tgggaccgag aagaggggtg cggacgcgcc 420  
 cagatcctcg gccttggggc tgctcggcag ccttggcgcg agtgccacgt cgagaggcgt 480  
 cggcggggag cgcggaaggg gacggcctgc gccaggccc aggtcaagcg ccttggtttg 540  
 cccactagga ttgttttaag aaaatggcag acaaaccaga catgggggaa atcgccagct 600  
 tcgataaggc caagctgaag aaaacggaga cgcaggagaa gaacaccctg ccgaccaaag 660  
 agagtgagtg tgcctcggtc tccgcgcccc agcccagccc ctcaccctgc tcttccttgc 720  
 aaaccocactc ctccaccccc caccgcgccc ttgtccccgg tgtgggcggc cccggcactc 780  
 tttcagtttc acaaagcgcc ttgtttctcc ccagcccaaa gcttccttct aaatcccaca 840  
 cctcgtggtg ctcatcacac cgggaagcac ctcggttgcg ggtggggggg tgcagcnccc 900  
 ctccagcgcc ccgttccgct tcaagccatt gagcaggaga agcggagtga aatttcctaa 960  
 gatcctggag gatttcttac ccccgtctc tcggagcacc ccagtcgctg atgtggagaa 1020  
 gagccaccct gcaagatgga cacgagtcca caagctgcac tgtgaacctg cgagcccgcg 1080  
 ccgatgccac cggcctgtgg tcgtctgaag ggaccccccc ccaatcggac tgccaaattc 1140  
 tcggtttgcc ccgggatatt atagaaaatt atttgtatga ataataaaaa taaaacacac 1200  
 ctcgttggca tggctggcgg tggctctgagt gttttagtta gtatgggtgc agtccactgc 1260  
 ag 1262

<210> 80  
 <211> 49  
 <212> PRT  
 <213> Homo sapiens

<400> 80  
 Asp Cys Phe Lys Lys Met Ala Asp Lys Pro Asp Met Gly Glu Ile Ala  
 1 5 10 15  
 Ser Phe Asp Lys Ala Lys Leu Lys Lys Thr Glu Thr Gln Glu Lys Asn  
 20 25 30  
 Thr Leu Pro Thr Lys Glu Thr Ile Glu Gln Glu Lys Arg Ser Glu Ile  
 35 40 45  
 Ser

<210> 81  
 <211> 1198  
 <212> DNA  
 <213> Homo sapiens

<400> 81  
 ttaaagtctc tcttcaccct gccgtcatgt ctaagtcaga gtctcctaaa gagcccgaac 60  
 agctgaggaa gctcttcatt ggagggttga gctttgaaac aactgatgag agcctgagga 120  
 gccattttga gcaatgggga acgctcacgg actgtgtggt aatgagagat ccaaacacca 180  
 agcgtcttag gggctttggg tttgtcacat atgccactgt ggaggagggt gatgcagcta 240  
 tgaatgcaag gccacacaag gtggatggaa gagttgtgga accaaagaga gctgtctcca 300

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gagaagattc tcaaagacca ggtgcccact taactgtgaa aaagatattt gttggtggca 360
ttaaagaaga cactgaagaa catcacctaa gagattattt tgaacagtat ggaaaaattg 420
aagtgattga aatcatgact gaccgaggca gtggcaagaa aaggggcttt gcctttgtaa 480
cctttgacga ccatgactcc gtggataaga ttgtcattca gaaataccat actgtgaatg 540
gccacaactg tgaagttaga aaagccctgt caaagcaaga gatggctagt gcttcatcca 600
gccaaagagg tcgaagtggg tctggaaact ttggtgggtg tctggagggt ggtttcgggtg 660
ggaatgacaa cttcggtcgt ggaggaaact tcagtgggtc tgggtggcttt ggtggcagcc 720
gtggtgggtg tggatatggt ggcagtgggg atggctataa tggatttggc aatgatggaa 780
gcaatttttg aggtggtgga agctacaatg attttgggaa ttacaacaat cagtcttcaa 840
attttggacc catgaaggga ggaaattttg gaggcagaag ctctggcccc tatggcgggtg 900
gaggccaata ctttgcaaaa ccacgaaacc aaggtggcta tggcgggttc agcagcagca 960
gtagctatgg cagtggcaga agattttaat tagggaggag tctgctacta gtcttatcag 1020
ctcttaaaaa cagaaactca tctgtccaag ttcgtggcag aaaggaacgt ccttgtgaag 1080
acctttatct gagccactgt acttcgttat cagccatgc agtttacatg agctgtttctg 1140
cagctcgaaa ttccattttg tgaatggggt ttttttttta ataaactgta ttttaactt 1198

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&lt;210&gt; 82

&lt;211&gt; 320

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 82

```

Met Ser Lys Ser Glu Ser Pro Lys Glu Pro Glu Gln Leu Arg Lys Leu
  1             5             10             15

Phe Ile Gly Gly Leu Ser Phe Glu Thr Thr Asp Glu Ser Leu Arg Ser
      20             25             30

His Phe Glu Gln Trp Gly Thr Leu Thr Asp Cys Val Val Met Arg Asp
      35             40             45

Pro Asn Thr Lys Arg Ser Arg Gly Phe Gly Phe Val Thr Tyr Ala Thr
      50             55             60

Val Glu Glu Val Asp Ala Ala Met Asn Ala Arg Pro His Lys Val Asp
      65             70             75             80

Gly Arg Val Val Glu Pro Lys Arg Ala Val Ser Arg Glu Asp Ser Gln
      85             90             95

Arg Pro Gly Ala His Leu Thr Val Lys Lys Ile Phe Val Gly Gly Ile
      100            105            110

Lys Glu Asp Thr Glu Glu His His Leu Arg Asp Tyr Phe Glu Gln Tyr
      115            120            125

Gly Lys Ile Glu Val Ile Glu Ile Met Thr Asp Arg Gly Ser Gly Lys
      130            135            140

Lys Arg Gly Phe Ala Phe Val Thr Phe Asp Asp His Asp Ser Val Asp
      145            150            155            160

Lys Ile Val Ile Gln Lys Tyr His Thr Val Asn Gly His Asn Cys Glu
      165            170            175

Val Arg Lys Ala Leu Ser Lys Gln Glu Met Ala Ser Ala Ser Ser Ser
      180            185            190

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Gln Arg Gly Arg Ser Gly Ser Gly Asn Phe Gly Gly Gly Arg Gly Gly  
 195 200 205

Gly Phe Gly Gly Asn Asp Asn Phe Gly Arg Gly Gly Asn Phe Ser Gly  
 210 215 220

Arg Gly Gly Phe Gly Gly Ser Arg Gly Gly Gly Gly Tyr Gly Gly Ser  
 225 230 235 240

Gly Asp Gly Tyr Asn Gly Phe Gly Asn Asp Gly Ser Asn Phe Gly Gly  
 245 250 255

Gly Gly Ser Tyr Asn Asp Phe Gly Asn Tyr Asn Asn Gln Ser Ser Asn  
 260 265 270

Phe Gly Pro Met Lys Gly Gly Asn Phe Gly Gly Arg Ser Ser Gly Pro  
 275 280 285

Tyr Gly Gly Gly Gly Gln Tyr Phe Ala Lys Pro Arg Asn Gln Gly Gly  
 290 295 300

Tyr Gly Gly Ser Ser Ser Ser Ser Tyr Gly Ser Gly Arg Arg Phe  
 305 310 315 320

<210> 83  
 <211> 1125  
 <212> DNA  
 <213> Homo sapiens

<400> 83  
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 aagatgtcag cccaggagag ctgcctcagc ctcacaaagt acttcctctt cgttttcaac 120  
 ctcttcttct tcgtcctcgg cagcctgac ttctgcttcg gcatctggat cctcatcgac 180  
 aagaccagct tcgtgtcctt tgtgggcttg gccttcgtgc ctctgcagat ctgggtccaaa 240  
 gtcttgccca tctcaggaat cttcaccatg ggcacgcgcc tcctgggttg tgtgggggcc 300  
 ctcaaggagc tccgctgcct cctgggcctg tattttggga tgctgctgct cctgtttgcc 360  
 acacagatca ccttggaat cctcatctcc actcagcggg cccagctgga gcgaagcttg 420  
 cgggacgtcg tagagaaaac catccaaaag tacggcacca accccgagga gaccgcggcc 480  
 gaggagagct gggactatgt gcagttccag ctgcgctgct gcggctggca ctaccgcag 540  
 gactgggtcc aagtccctcat cctgagaggt aacgggtcgg aggcgcaccg cgtgccctgc 600  
 tcctgctaca acttgctcggc gaccaacgac tccacaatcc tagataaggt gatcttgccc 660  
 cagctcagca ggcttgaca cctggcgcgg tccagacaca gtgcagacat ctgcgctgtc 720  
 cctgcagaga gccacatcta ccgcgagggc tgccgcgagg gcctccagaa gtggctgcac 780  
 aacaacctta tttccatagt gggcatttgc ctggcgctcg gcctactcga gctcgggttc 840  
 atgacgctct cgatattcct gtgcagaaac ctggaccaag tctacaaccg gctcgtcga 900  
 taccgttagg ccccgccctc cccaaagtcc cgcgccgcc ccgtcacgtg cgtggggcac 960  
 ttccctgctg cctgtaaata tttgtttaat cccagttcg cctggagccc tccgccttca 1020  
 cattccccctg gggaccacag tggctgcgtg cccctgctgc tgtcacctct cccacgggac 1080  
 ctggggcttt cgtccacagc ttctgtctcc catctgtcgg cctac 1125

<210> 84  
 <211> 281

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&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 84

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ser | Ala | Gln | Glu | Ser | Cys | Leu | Ser | Leu | Ile | Lys | Tyr | Phe | Leu | Phe | 1   | 5   | 10  | 15  |
| Val | Phe | Asn | Leu | Phe | Phe | Phe | Val | Leu | Gly | Ser | Leu | Ile | Phe | Cys | Phe | 20  | 25  | 30  |     |
| Gly | Ile | Trp | Ile | Leu | Ile | Asp | Lys | Thr | Ser | Phe | Val | Ser | Phe | Val | Gly | 35  | 40  | 45  |     |
| Leu | Ala | Phe | Val | Pro | Leu | Gln | Ile | Trp | Ser | Lys | Val | Leu | Ala | Ile | Ser | 50  | 55  | 60  |     |
| Gly | Ile | Phe | Thr | Met | Gly | Ile | Ala | Leu | Leu | Gly | Cys | Val | Gly | Ala | Leu | 65  | 70  | 75  | 80  |
| Lys | Glu | Leu | Arg | Cys | Leu | Leu | Gly | Leu | Tyr | Phe | Gly | Met | Leu | Leu | Leu | 85  | 90  | 95  |     |
| Leu | Phe | Ala | Thr | Gln | Ile | Thr | Leu | Gly | Ile | Leu | Ile | Ser | Thr | Gln | Arg | 100 | 105 | 110 |     |
| Ala | Gln | Leu | Glu | Arg | Ser | Leu | Arg | Asp | Val | Val | Glu | Lys | Thr | Ile | Gln | 115 | 120 | 125 |     |
| Lys | Tyr | Gly | Thr | Asn | Pro | Glu | Glu | Thr | Ala | Ala | Glu | Glu | Ser | Trp | Asp | 130 | 135 | 140 |     |
| Tyr | Val | Gln | Phe | Gln | Leu | Arg | Cys | Cys | Gly | Trp | His | Tyr | Pro | Gln | Asp | 145 | 150 | 155 | 160 |
| Trp | Phe | Gln | Val | Leu | Ile | Leu | Arg | Gly | Asn | Gly | Ser | Glu | Ala | His | Arg | 165 | 170 | 175 |     |
| Val | Pro | Cys | Ser | Cys | Tyr | Asn | Leu | Ser | Ala | Thr | Asn | Asp | Ser | Thr | Ile | 180 | 185 | 190 |     |
| Leu | Asp | Lys | Val | Ile | Leu | Pro | Gln | Leu | Ser | Arg | Leu | Gly | His | Leu | Ala | 195 | 200 | 205 |     |
| Arg | Ser | Arg | His | Ser | Ala | Asp | Ile | Cys | Ala | Val | Pro | Ala | Glu | Ser | His | 210 | 215 | 220 |     |
| Ile | Tyr | Arg | Glu | Gly | Cys | Ala | Gln | Gly | Leu | Gln | Lys | Trp | Leu | His | Asn | 225 | 230 | 235 | 240 |
| Asn | Leu | Ile | Ser | Ile | Val | Gly | Ile | Cys | Leu | Gly | Val | Gly | Leu | Leu | Glu | 245 | 250 | 255 |     |
| Leu | Gly | Phe | Met | Thr | Leu | Ser | Ile | Phe | Leu | Cys | Arg | Asn | Leu | Asp | His | 260 | 265 | 270 |     |
| Val | Tyr | Asn | Arg | Leu | Ala | Arg | Tyr | Arg | 275 | 280 |     |     |     |     |     |     |     |     |     |

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<210> 85  
 <211> 1216  
 <212> DNA  
 <213> Homo sapiens

<400> 85  
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 ggtgctgagc tccccactgg ctttggctgg ggacaccgga ccatgtttct tgcagcagga 180  
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 agactggacc ttccagattc tggatgatgt ggaacagatt cctcggagtg gagagggtta 660  
 cacctgccaa gtggagcacc caagcgtgac gagccctctc acagtggaat ggagagcaca 720  
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<210> 86  
 <211> 266  
 <212> PRT  
 <213> Homo sapiens

<400> 86  
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 20 25 30  
 Arg Pro Cys Phe Leu Gln Gln Asp Lys Tyr Glu Cys His Phe Phe Asn  
 35 40 45  
 Gly Thr Glu Arg Val Arg Phe Leu His Arg Gly Ile Tyr Asn Gln Gln  
 50 55 60  
 Glu Asn Val Arg Phe Asp Ser Asp Val Gly Glu Tyr Arg Ala Val Thr  
 65 70 75 80  
 Glu Leu Gly Arg Pro Asp Ala Glu Tyr Trp Asn Ser Gln Lys Asp Ile  
 85 90 95  
 Leu Glu Gln Ala Arg Ala Ala Val Asp Thr Tyr Cys Arg His Asn Tyr  
 100 105 110

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Gly Ala Val Glu Ser Phe Thr Val Gln Arg Arg Val Glu Pro Lys Val  
 115 120 125  
 Thr Val Tyr Pro Ala Arg Thr Gln Thr Leu Gln His His Asn Leu Leu  
 130 135 140  
 Val Cys Ser Val Asn Gly Phe Tyr Pro Gly Ser Ile Glu Val Arg Trp  
 145 150 155 160  
 Phe Arg Asn Gly Gln Glu Glu Lys Ala Gly Val Val Ser Thr Gly Leu  
 165 170 175  
 Ile Gln Asn Gly Asp Trp Thr Phe Gln Ile Leu Val Met Leu Glu Thr  
 180 185 190  
 Val Pro Arg Ser Gly Glu Val Tyr Thr Cys Gln Val Glu His Pro Ser  
 195 200 205  
 Val Thr Ser Pro Leu Thr Val Glu Trp Arg Ala Gln Ser Glu Ser Ala  
 210 215 220  
 Gln Ser Lys Met Leu Ser Gly Ile Gly Gly Phe Val Leu Gly Leu Leu  
 225 230 235 240  
 Phe Leu Gly Ala Gly Leu Phe Ile Tyr Phe Lys Asn Gln Lys Gly His  
 245 250 255  
 Ser Gly Leu His Pro Thr Gly Leu Val Ser  
 260 265

&lt;210&gt; 87

&lt;211&gt; 1881

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 87

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gccatggagg caacctacat caaccacaat ttctcccagc agtgcttgag aatggggaag 1080
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atgcctctg ttgcgtaccg ttaccgcagg tggaagcttg gagatgatat tgaccttatt 1200
gtccgttgtg agcacgatgg cgtcatgact ggagccaacg gggaagtgtc cttcatcaac 1260

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atcaagacac tcaatgagtg ggattccagg cactgtaatg gcgttgactg gcgtcagaag 1320
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gcccgggtgga cctgctgtgc tttgctggct ggatctgagt acctcaagct tggttatgtg 1440
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tgtgtctaac ttgctctctg acatttagca gatgaaataa aatatatatac tgtttagtct 1860
tttaaaaaaa aaaaaaaaaa a 1881

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&lt;210&gt; 88

&lt;211&gt; 548

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 88

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Met Ala Lys Phe Met Thr Pro Val Ile Gln Asp Asn Pro Ser Gly Trp
  1             5             10             15

Gly Pro Cys Ala Val Pro Glu Gln Phe Arg Asp Met Pro Tyr Gln Pro
             20             25             30

Phe Ser Lys Gly Asp Arg Leu Gly Lys Val Ala Asp Trp Thr Gly Ala
  35             40             45

Thr Tyr Gln Asp Lys Arg Tyr Thr Asn Lys Tyr Ser Ser Gln Phe Gly
  50             55             60

Gly Gly Ser Gln Tyr Ala Tyr Phe His Glu Glu Asp Glu Ser Ser Phe
  65             70             75             80

Gln Leu Val Asp Thr Ala Arg Thr Gln Lys Thr Ala Tyr Gln Arg Asn
             85             90             95

Arg Met Arg Phe Ala Gln Arg Asn Leu Arg Arg Asp Lys Asp Arg Arg
 100             105             110

Asn Met Leu Gln Phe Asn Leu Gln Ile Leu Pro Lys Ser Ala Lys Gln
 115             120             125

Lys Glu Arg Glu Arg Ile Arg Leu Gln Lys Lys Phe Gln Lys Gln Phe
 130             135             140

Gly Val Arg Gln Lys Trp Asp Gln Lys Ser Gln Lys Pro Arg Asp Ser
 145             150             155             160

Ser Val Glu Val Arg Ser Asp Trp Glu Val Lys Glu Glu Met Asp Phe
             165             170             175

Pro Gln Leu Met Lys Met Arg Tyr Leu Glu Val Ser Glu Pro Gln Asp
 180             185             190

Ile Glu Cys Cys Gly Ala Leu Glu Tyr Tyr Asp Lys Ala Phe Asp Arg
 195             200             205

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Thr | Thr | Arg | Ser | Glu | Lys | Pro | Leu | Arg | Ser | Ile | Lys | Arg | Ile | Phe |
| 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| His | Thr | Val | Thr | Thr | Thr | Asp | Asp | Pro | Val | Ile | Arg | Lys | Leu | Ala | Lys |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Thr | Gln | Gly | Asn | Val | Phe | Ala | Thr | Asp | Ala | Ile | Leu | Ala | Thr | Leu | Met |
|     |     |     | 245 |     |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Ser | Cys | Thr | Arg | Ser | Val | Tyr | Ser | Trp | Asp | Ile | Val | Val | Gln | Arg | Val |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Gly | Ser | Lys | Leu | Phe | Phe | Asp | Lys | Arg | Asp | Asn | Ser | Asp | Phe | Asp | Leu |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Leu | Thr | Val | Ser | Glu | Thr | Ala | Asn | Glu | Pro | Pro | Gln | Asp | Glu | Gly | Asn |
| 290 |     |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Ser | Phe | Asn | Ser | Pro | Arg | Asn | Leu | Ala | Met | Glu | Ala | Thr | Tyr | Ile | Asn |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| His | Asn | Phe | Ser | Gln | Gln | Cys | Leu | Arg | Met | Gly | Lys | Glu | Arg | Tyr | Asn |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Phe | Pro | Asn | Pro | Asn | Pro | Phe | Val | Glu | Asp | Asp | Met | Asp | Lys | Asn | Glu |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Ile | Ala | Ser | Val | Ala | Tyr | Arg | Tyr | Arg | Arg | Trp | Lys | Leu | Gly | Asp | Asp |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Ile | Asp | Leu | Ile | Val | Arg | Cys | Glu | His | Asp | Gly | Val | Met | Thr | Gly | Ala |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Asn | Gly | Glu | Val | Ser | Phe | Ile | Asn | Ile | Lys | Thr | Leu | Asn | Glu | Trp | Asp |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Ser | Arg | His | Cys | Asn | Gly | Val | Asp | Trp | Arg | Gln | Lys | Leu | Asp | Ser | Gln |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Arg | Gly | Ala | Val | Ile | Ala | Thr | Glu | Leu | Lys | Asn | Asn | Ser | Tyr | Lys | Leu |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Ala | Arg | Trp | Thr | Cys | Cys | Ala | Leu | Leu | Ala | Gly | Ser | Glu | Tyr | Leu | Lys |
|     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Leu | Gly | Tyr | Val | Ser | Arg | Tyr | His | Val | Lys | Asp | Ser | Ser | Arg | His | Val |
|     |     | 450 |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Ile | Leu | Gly | Thr | Gln | Gln | Phe | Lys | Pro | Asn | Glu | Phe | Ala | Ser | Gln | Ile |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Asn | Leu | Ser | Val | Glu | Asn | Ala | Trp | Gly | Ile | Leu | Arg | Cys | Val | Ile | Asp |
|     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |
| Ile | Cys | Met | Lys | Leu | Glu | Glu | Gly | Lys | Tyr | Leu | Ile | Leu | Lys | Asp | Pro |
|     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |

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Asn Lys Gln Val Ile Arg Val Tyr Ser Leu Pro Asp Gly Thr Phe Ser  
 515 520 525

Ser Asp Glu Asp Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu  
 530 535 540

Glu Glu Glu Thr  
 545

<210> 89  
 <211> 670  
 <212> DNA  
 <213> Homo sapiens

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 gaagaactgg ttgactacaa gtcttgtgct catgactggg tctatgaata agaggtggac 540  
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<210> 90  
 <211> 152  
 <212> PRT  
 <213> Homo sapiens

<400> 90  
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 Phe Arg Leu Val Ala Met Lys Phe Leu Arg Ala Ser Glu Glu His Leu  
 35 40 45  
 Lys Gln His Tyr Ile Asp Leu Lys Asp Arg Pro Phe Phe Pro Gly Leu  
 50 55 60  
 Val Lys Tyr Met Asn Ser Gly Pro Val Val Ala Met Val Trp Glu Gly  
 65 70 75 80  
 Leu Asn Val Val Lys Thr Gly Arg Val Met Leu Gly Glu Thr Asn Pro  
 85 90 95  
 Ala Asp Ser Lys Pro Gly Thr Ile Arg Gly Asp Phe Cys Ile Gln Val  
 100 105 110

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Gly Arg Asn Ile Ile His Gly Ser Asp Ser Val Lys Ser Ala Glu Lys  
 115 120 125

Glu Ile Ser Leu Trp Phe Lys Pro Glu Glu Leu Val Asp Tyr Lys Ser  
 130 135 140

Cys Ala His Asp Trp Val Tyr Glu  
 145 150

<210> 91  
 <211> 1097  
 <212> \DNA  
 <213> Homo sapiens

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 tgggcaagaa caccatgatg cgcaaggcca tccgagggca cctggaaaac aaccagctc 300  
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 cagctaaggt tgaagccaag gaagagtcgg aggagtcgga cgaggatatg ggatttggtc 1020  
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 taaaggctta cttcttt 1097

<210> 92  
 <211> 317  
 <212> PRT  
 <213> Homo sapiens

<400> 92  
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 Asp Asn Val Gly Ser Lys Gln Met Gln Gln Ile Arg Met Ser Leu Arg  
 35 40 45  
 Gly Lys Ala Val Val Leu Met Gly Lys Asn Thr Met Met Arg Lys Ala  
 50 55 60  
 Ile Arg Gly His Leu Glu Asn Asn Pro Ala Leu Glu Lys Leu Leu Pro  
 65 70 75 80

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His Ile Arg Gly Asn Val Gly Phe Val Phe Thr Lys Glu Asp Leu Thr  
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 Glu Ile Arg Asp Met Leu Leu Ala Asn Lys Val Pro Ala Ala Ala Arg  
                             100                            105                            110  
 Ala Gly Ala Ile Ala Pro Cys Glu Val Thr Val Pro Ala Gln Asn Thr  
                             115                            120                            125  
 Gly Leu Gly Pro Glu Lys Thr Ser Phe Phe Gln Ala Leu Gly Ile Thr  
                             130                            135                            140  
 Thr Lys Ile Ser Arg Gly Thr Ile Glu Ile Leu Ser Asp Val Gln Leu  
                             145                            150                            155                            160  
 Ile Lys Thr Gly Asp Lys Val Gly Ala Ser Glu Ala Thr Leu Leu Asn  
                             165                            170                            175  
 Met Leu Asn Ile Ser Pro Phe Ser Phe Gly Leu Val Ile Gln Gln Val  
                             180                            185                            190  
 Phe Asp Asn Gly Ser Ile Tyr Asn Pro Glu Val Leu Asp Ile Thr Glu  
                             195                            200                            205  
 Glu Thr Leu His Ser Arg Phe Leu Glu Gly Val Arg Asn Val Ala Ser  
                             210                            215                            220  
 Val Cys Leu Gln Ile Gly Tyr Pro Thr Val Ala Ser Val Pro His Ser  
                             225                            230                            235                            240  
 Ile Ile Asn Gly Tyr Lys Arg Val Leu Ala Leu Ser Val Glu Thr Asp  
                             245                            250                            255  
 Tyr Thr Phe Pro Leu Ala Glu Lys Val Lys Ala Phe Leu Ala Asp Pro  
                             260                            265                            270  
 Ser Ala Phe Val Ala Ala Ala Pro Val Ala Ala Ala Thr Thr Ala Ala  
                             275                            280                            285  
 Pro Ala Ala Ala Ala Ala Pro Ala Lys Val Glu Ala Lys Glu Glu Ser  
                             290                            295                            300  
 Glu Glu Ser Asp Glu Asp Met Gly Phe Gly Leu Phe Asp  
                             305                            310                            315

&lt;210&gt; 93

&lt;211&gt; 6711

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 93

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ccgaggggggt agctgggact acaggtgcgc accaccatgc ccagctaatt ttgtattttt 240
cgtagagatg gggtttcacc atgttgcca ggctggtcct gaactcctga cctcaggtga 300
tcctcccgcc tcggcctccc aaagtgtgga aattacaggc gtgatccacc gcaccgggcc 360

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|-------------|-------------|------------|------------|------------|-------------|------|
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| gcccactaca  | gcctcgacct  | ccggggtcaa | gcaatcctcc | ccgcccagcc | tcctgagtag  | 480  |
| cgagcgccctc | gacgcccagc  | taatttttat | ttttatttat | ttttttgtag | agacggcgctc | 540  |
| tctctaagat  | gcccaggctg  | gtggccggtg | tcgaactcct | aagatgaagc | gatcctcccc  | 600  |
| ggccttggcc  | tccgcgcctc  | ctaaagcgcc | aggtatgagc | caccgcgcct | ggcctacaag  | 660  |
| tgcatttttaa | ttaaagtatt  | attaatgtct | ttgcctgaag | aaattcgctt | ttaaattgtg  | 720  |
| acttatcttt  | cacccaaaaa  | tcaaagcaca | attcagcccc | gaggcggggg | cggtaggagc  | 780  |
| tgggcggggc  | gggggcaggg  | aaagaccagg | agcagagatt | caaaaagagt | aagagggcaa  | 840  |
| aatgtgcata  | atgcatcttc  | acaggtaaga | gcctggccag | gtcctgtttt | taatggcttc  | 900  |
| ctcctgaaga  | agattcaagc  | agagtgtaa  | atattttcgg | aaagtagagc | attttgaaag  | 960  |
| catttcataa  | tctctcaaaa  | ccggagactg | ctcctgtccc | acctcgtag  | agaaaacagc  | 1020 |
| gatgtcctaaa | ggcaacctcc  | ttcctgacat | tgcttggtag | gacgcgacgt | ggtgttttgc  | 1080 |
| cgcgcggaat  | gcggacgcaa  | ggctgtcct  | aggtctcggg | gacgcgccat | ccccatttcc  | 1140 |
| gctcgcggag  | gcgtagggtc  | cgggcgcggg | accccagtcg | accttgactg | gcggcgcgac  | 1200 |
| cttgaggcct  | gcgttcgcct  | cagttgcccc | ctctgtgcaa | tgaggagacg | cgctcatcg   | 1260 |
| cttgacaacg  | gccgaagagc  | cgccgcgctt | ccgtctcccc | cgtgcgcgcg | ccatgctgcc  | 1320 |
| cacccccggt  | ccgcaactgac | cctcccccg  | gccccgcgct | ccgtactgcc | gccccgcccc  | 1380 |
| gagtccecatg | ccgcagccac  | cgcgacggag | cccgaggcg  | ggaacctgcc | tcgcgcgctt  | 1440 |
| agcgcgcacg  | cgcgcctcat  | gtgtcgtccc | catcagcgcc | ggcttcctgc | tataggccag  | 1500 |
| atgcatgtgc  | actctggcga  | agtcgcagac | ccgattggcc | gggacggagg | cgcgagaccg  | 1560 |
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&lt;400&gt; 98

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catcaaagtg gagatatgtt aactattgta taatgtggcc tgttatacat gacactcttc 1260
tgaattgact gtatttccagt gagctgcccc caaatcaagt ttagtgccct catccattta 1320
tgtctcagac cgctattcct aactattcaa tggtagagcag actgcaaata tgccctgatag 1380
gacctatatt cccacagcac taattcaaca tatatcttac tgagagcatg ttttatcatt 1440
accattaaga agttaaatga acatcagaat ttaaaatcat aaatataatc taatacactt 1500
t

```

&lt;210&gt; 99

&lt;211&gt; 258

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 99

```

Met Met Val Leu Gln Val Ser Ala Ala Pro Arg Thr Val Ala Leu Thr
  1                      5                      10                      15

```

```

Ala Leu Leu Met Val Leu Leu Thr Ser Val Val Gln Gly Arg Ala Thr
      20                      25                      30

```

```

Pro Glu Asn Tyr Val Tyr Gln Gly Arg Gln Glu Cys Tyr Ala Phe Asn
      35                      40                      45

```

```

Gly Thr Gln Arg Phe Leu Glu Arg Tyr Ile Tyr Asn Arg Glu Glu Tyr
      50                      55                      60

```

```

Ala Arg Phe Asp Ser Asp Val Gly Glu Phe Arg Ala Val Thr Glu Leu
      65                      70                      75                      80

```

```

Gly Arg Pro Ala Ala Glu Tyr Trp Asn Ser Gln Lys Asp Ile Leu Glu
      85                      90                      95

```

```

Glu Lys Arg Ala Val Pro Asp Arg Val Cys Arg His Asn Tyr Glu Leu
      100                     105                     110

```

```

Asp Glu Ala Val Thr Leu Gln Arg Arg Val Gln Pro Lys Val Asn Val
      115                     120                     125

```

```

Ser Pro Ser Lys Lys Gly Pro Leu Gln His His Asn Leu Leu Val Cys
      130                     135                     140

```

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His Val Thr Asp Phe Tyr Pro Gly Ser Ile Gln Val Arg Trp Phe Leu  
145 150 155 160

Asn Gly Gln Glu Glu Thr Ala Gly Val Val Ser Thr Asn Leu Ile Arg  
165 170 175

Asn Gly Asp Trp Thr Phe Gln Ile Leu Val Met Leu Glu Met Thr Pro  
180 185 190

Gln Gln Gly Asp Val Tyr Ile Cys Gln Val Glu His Thr Ser Leu Asp  
195 200 205

Ser Pro Val Thr Val Glu Trp Lys Ala Gln Ser Asp Ser Ala Gln Ser  
210 215 220

Lys Thr Leu Thr Gly Ala Gly Gly Phe Val Leu Gly Leu Ile Ile Cys  
225 230 235 240

Gly Val Gly Ile Phe Met His Arg Arg Ser Lys Lys Val Gln Arg Gly  
245 250 255

Ser Ala

<210> 100

<211> 5022

<212> DNA

<213> Homo sapiens

<400> 100

```

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gaggacgcgg gcgaggaaga ccagcccgcg ggccccgatg ttgtgactgt gacagactca 120
ctgggggtttg tacatgctgg ggaggagcct tcctttcagg ggtgaccaca ttcactctggg 180
catgcctgca gtactcttgg cccatggacc tgaaggagaa gcacctgggc gagcctccct 240
cagccctggg cctgtccacg cggaaggccc tcagcgtcct gaaggagcag ctggaggcag 300
tgctggaagg acatctcagg gagcggaaga agtgtctgac gtggaaggag gtgtggagaa 360
gcagcttcct ccaccacagt aaccgctgct cctgcttcca ctggccgggg gcctcactca 420
tgctactggc cgtgctgctg ctgctgggct gctgcggggg acagccagcc gggagccgtg 480
gggtggggct ggtgaatgcc tcggccttgt tcctgttact gcttctcaac cttgtgctca 540
tcgggcggca agaccggctg aagcgtcggg aggtagagcg gaggtgcga gggatcattg 600
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cagacctcca catgcctttt gcgccatcct ggtccttgca ctgggcctac agagacggac 720
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ggccacagag cccccagcag caccggcttt tccgtgtcct tgagaccctt gtgattgaca 960
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tctgggttct ggcaactgcc tgtggagagg cccgtgtcct ggcccagatg agcaaggcct 1260
caccagctc cctgctggct aagtctcag aggatactct cagcagctat acggaggctg 1320
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tgttcttcag cgggaagggtg gagccccctc acagcagcca tgaggacctc accgatggcc 1560
tatccaccgg ctcttctgc catcccagac cccatgaacg agacgccctc ctggctggct 1620

```

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|             |            |             |             |             |             |      |
|-------------|------------|-------------|-------------|-------------|-------------|------|
| ccttgaacaa  | caccctgcac | ctttccaatg  | agcaggagcg  | tggcgactgg  | cctggcgagg  | 1680 |
| ctcccaagcc  | ccccgagccc | tattcacacc  | acaaagcgca  | tggccgcagc  | aaacacccat  | 1740 |
| ctggctccaa  | cgtgagcttc | agcagggaca  | ccgagggtgg  | tgaagaagag  | cccagcaaga  | 1800 |
| cccagcctgg  | gatggagagc | gacccctacg  | aagcagagga  | ctttgtgtgt  | gactaccacc  | 1860 |
| tggagatgct  | gagcctgtcc | caggaccagc  | agaacccctc  | ctgcatccag  | tttgatgact  | 1920 |
| ccaactggca  | gctgcacctc | acctccctca  | aacccctggg  | cctcaatgtg  | ctgctgaacc  | 1980 |
| tgtgtgatgc  | cagcgtcacc | gagcgcctgt  | gccgattctc  | cgaccacctg  | tgcaacattg  | 2040 |
| ccttgcaaga  | gagccacagc | gccgtgctgc  | ccgtccatgt  | gcoctggggc  | ctctgcgagc  | 2100 |
| ttgcccgcct  | cattggcttc | actcctgggg  | ccaaggagct  | tttcaagcag  | gagaaccatc  | 2160 |
| tggcgctgta  | ccgcctcccc | agtgccgaga  | caatgaagga  | gacatcgctg  | gggcggctct  | 2220 |
| cctgtgtcac  | caagcggcgg | cctccctcca  | gccacatgat  | cagcctcttc  | attaaagaca  | 2280 |
| ccaccaccag  | cacagagcag | atgctgtccc  | atggcacccg  | tgatgtggtc  | ttagaggcct  | 2340 |
| gcacagactt  | ctgggacgga | gctgacatct  | accctctctc  | gggatctgac  | agaaaagaaag | 2400 |
| tgttggaact  | ctaccagcga | gcctgcctgt  | ctgggtattg  | ctctgccttc  | gcctacaagc  | 2460 |
| ccatgaactg  | cgccctgtcc | tctcagctca  | atggcaagtg  | catcgagctg  | gtacaggtgc  | 2520 |
| ccggccaaag  | cagcatcttc | accatgtgcg  | agctgcccag  | caccatcccc  | atcaagcaga  | 2580 |
| acgcccgcgc  | cagcagctgg | agctctgacg  | aagggatcgg  | ggaggtgctg  | gagaagggaag | 2640 |
| actgcatgca  | ggccctgagc | ggccagatct  | tcatgggcat  | ggtgtccctc  | cagtaccagg  | 2700 |
| ccggcttgga  | catcgtgcgc | ctcattgatg  | ggcttgtcaa  | cgctgccttc  | cgctttgtct  | 2760 |
| acttctcttt  | ggaggatgag | ctcaaaaagca | agggtgttgc  | agaaaaaatg  | ggcctggaga  | 2820 |
| caggctggaa  | ctgccacatc | tccctcacac  | ccaatggtga  | catgcctggc  | tccagatccc  | 2880 |
| ccccctccag  | ccccagccac | gcaggctccc  | tgcattgatg  | cctgaatcag  | gtgtcccag   | 2940 |
| atgatgcaga  | agggctcctc | ctcatggagg  | aggagggcc   | ctcgacctc   | atcagcttcc  | 3000 |
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| tccagagcga  | catcagcatt | gccctggatc  | ccctgtaccc  | atcccgttgc  | tcctgggaga  | 3300 |
| cttttggtcta | cgccaccagc | atcagcatgg  | cccaggcctc  | ggatggcctt  | tctccctgc   | 3360 |
| agctgtcagg  | gcagctcaac | agcctgcctc  | gttccctgac  | ctttcgccag  | gaggagacca  | 3420 |
| tcagcatcat  | ccggcttata | gaacaggctc  | ggcatgccac  | ctatggcatc  | cgtaagtgtc  | 3480 |
| tcctcttctc  | gctgcagtgc | cagctgactc  | ttgtggctcat | ccagttcctt  | tcttgccctg  | 3540 |
| tccagctgcc  | gccactcctg | agtaccaccg  | acatcctgtg  | gctgtcctgc  | ttttgctacc  | 3600 |
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| cggggaaaaa  | cctccagctc | attcccaaga  | agaccagca   | ctacttctctg | ctctgcttcc  | 3720 |
| tgtctcaagtt | cagcctcacc | atcagctcct  | gcctcatctg  | ctttggcttc  | acactgcaga  | 3780 |
| gcttctgtga  | cagctcccgg | gaccgcaacc  | tcaccaactg  | ctcctccgtc  | atgctgcca   | 3840 |
| gcaacgacga  | cagggtcca  | gcctggtttg  | aggactttgc  | caatggactg  | ctgtcggctc  | 3900 |
| agaagctcac  | ggccgcctg  | attgtcctgc  | acactgtctt  | catttccatc  | acccatgtgc  | 3960 |
| atcgaccaa   | gccccgtgtg | agaaaagagc  | ccttgacca   | cctctgggtg  | gccgtgacag  | 4020 |
| tgcctgtgggt | gctgctgggt | caggtggctc  | agacggctgt  | ggacctgcag  | ctgtggacac  | 4080 |
| acagggacag  | ccacgtccac | tttgccctgg  | aggacgtgcc  | cctgctgaca  | tggctcctgg  | 4140 |
| gctgcctgtc  | cctggctcct | gtgggtggta  | ccaatgagat  | cgtgaagcta  | catgagattc  | 4200 |
| gggtccgagt  | ccgtaccag  | aagcgacaga  | agctgcagtt  | tgaactaag   | ctgggcatga  | 4260 |
| actctccctt  | ctgagccact | ggctgtgggt  | gctgtagttg  | cccccgctcc  | tggggctaaa  | 4320 |
| gccagaccca  | tttctgaaca | ggggagtgtg  | tatcatgaat  | gtttccaggt  | ttgctcctgc  | 4380 |
| acccgtggca  | ctggaaaccc | agctccccgt  | gtcagacccc  | gctgtcttcc  | tgagccctgg  | 4440 |
| ggctcactgt  | ggaggagctg | acggcctggg  | cccttggcca  | gtcctggctc  | ttccctgggc  | 4500 |
| ctcaccagg   | acactcttga | atgtatggcc  | tcaggcgctc  | cctagagggg  | ccctaaccac  | 4560 |
| cctcacctgt  | gagctacccc | ctttagggat  | cccttgcccc  | cttgagatc   | ccttgcccc   | 4620 |
| cagtgcctct  | gctcgtgggt | ccctggacac  | ggccttgaag  | ccaaccttct  | ttggaggagc  | 4680 |
| aacagcagca  | gccttggccg | acgcgtccaa  | ctcccaaggc  | tgcctgggag  | ggcagggggg  | 4740 |
| tgggtgcttg  | ctggatgtgg | ccccgagtgc  | ctccctcccc  | tcctctgtg   | ggggagtctc  | 4800 |
| ccgcctgaac  | ctgaagatgg | agcaggggcc  | ccgcttcgcc  | ctggagcctc  | ttcctgtgcc  | 4860 |
| tggctcaagc  | tggctgcctg | tcagtcttgg  | ggaatctggc  | ccaggtctcc  | tcagcctctg  | 4920 |
| cccagttct   | gggagaagtt | tctactgggt  | tatatTTTTT  | actggaaatg  | agccttttag  | 4980 |
| gaatgaatgt  | agactgggtt | gtattaaaa   | gtgtcaattg  | ct          |             | 5022 |



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&lt;210&gt; 101

&lt;211&gt; 1356

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 101

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Asp | Leu | Lys | Glu | Lys | His | Leu | Gly | Glu | Pro | Pro | Ser | Ala | Leu | Gly |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Ser | Thr | Arg | Lys | Ala | Leu | Ser | Val | Leu | Lys | Glu | Gln | Leu | Glu | Ala |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Leu | Glu | Gly | His | Leu | Arg | Glu | Arg | Lys | Lys | Cys | Leu | Thr | Trp | Lys |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Val | Trp | Arg | Ser | Ser | Phe | Leu | His | His | Ser | Asn | Arg | Cys | Ser | Cys |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | His | Trp | Pro | Gly | Ala | Ser | Leu | Met | Leu | Leu | Ala | Val | Leu | Leu | Leu |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Gly | Cys | Cys | Gly | Gly | Gln | Pro | Ala | Gly | Ser | Arg | Gly | Val | Gly | Leu |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Asn | Ala | Ser | Ala | Leu | Phe | Leu | Leu | Leu | Leu | Leu | Asn | Leu | Val | Leu |
|     |     | 100 |     |     |     |     | 105 |     |     |     |     |     | 110 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Gly | Arg | Gln | Asp | Arg | Leu | Lys | Arg | Arg | Glu | Val | Glu | Arg | Arg | Leu |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Gly | Ile | Ile | Asp | Gln | Ile | Gln | Asp | Ala | Leu | Arg | Asp | Gly | Arg | Glu |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Gln | Trp | Pro | Ser | Ala | Met | Tyr | Pro | Asp | Leu | His | Met | Pro | Phe | Ala |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Ser | Trp | Ser | Leu | His | Trp | Ala | Tyr | Arg | Asp | Gly | His | Leu | Val | Asn |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Pro | Val | Ser | Leu | Leu | Val | Glu | Gly | Asp | Ile | Ile | Ala | Leu | Arg | Pro |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Gln | Glu | Ser | Phe | Ala | Ser | Leu | Arg | Gly | Ile | Lys | Asp | Asp | Glu | His |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Val | Leu | Glu | Pro | Gly | Asp | Leu | Phe | Pro | Pro | Phe | Ser | Pro | Pro | Pro |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Pro | Arg | Gly | Glu | Val | Glu | Arg | Gly | Pro | Gln | Ser | Pro | Gln | Gln | His |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Leu | Phe | Arg | Val | Leu | Glu | Thr | Pro | Val | Ile | Asp | Asn | Ile | Arg | Trp |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Leu | Asp | Met | Ala | Leu | Ser | Arg | Pro | Val | Thr | Ala | Leu | Asp | Asn | Glu |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Phe | Thr | Val | Gln | Ser | Val | Met | Leu | His | Tyr | Ala | Val | Pro | Val | Val |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Leu | Ala | Gly | Phe | Leu | Ile | Thr | Asn | Ala | Leu | Arg | Phe | Ile | Phe | Ser | Ala |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Pro | Gly | Val | Thr | Ser | Trp | Gln | Tyr | Thr | Leu | Leu | Gln | Leu | Gln | Val | Asn |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Gly | Val | Leu | Pro | Ile | Leu | Pro | Leu | Leu | Phe | Pro | Val | Leu | Trp | Val | Leu |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Ala | Thr | Ala | Cys | Gly | Glu | Ala | Arg | Val | Leu | Ala | Gln | Met | Ser | Lys | Ala |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Ser | Pro | Ser | Ser | Leu | Leu | Ala | Lys | Phe | Ser | Glu | Asp | Thr | Leu | Ser | Ser |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Tyr | Thr | Glu | Ala | Val | Ser | Ser | Gln | Glu | Met | Leu | Arg | Cys | Ile | Trp | Gly |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| His | Phe | Leu | Arg | Val | Leu | Gly | Gly | Thr | Ser | Pro | Thr | Leu | Ser | His | Ser |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Ser | Ser | Leu | Leu | His | Ser | Leu | Gly | Ser | Val | Thr | Val | Leu | Cys | Cys | Val |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Asp | Lys | Gln | Gly | Ile | Leu | Ser | Trp | Pro | Asn | Pro | Ser | Pro | Glu | Thr | Val |
|     |     | 420 |     |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Leu | Phe | Phe | Ser | Gly | Lys | Val | Glu | Pro | Pro | His | Ser | Ser | His | Glu | Asp |
|     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Leu | Thr | Asp | Gly | Leu | Ser | Thr | Arg | Ser | Phe | Cys | His | Pro | Glu | Pro | His |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Glu | Arg | Asp | Ala | Leu | Leu | Ala | Gly | Ser | Leu | Asn | Asn | Thr | Leu | His | Leu |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Ser | Asn | Glu | Gln | Glu | Arg | Gly | Asp | Trp | Pro | Gly | Glu | Ala | Pro | Lys | Pro |
|     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |
| Pro | Glu | Pro | Tyr | Ser | His | His | Lys | Ala | His | Gly | Arg | Ser | Lys | His | Pro |
|     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| Ser | Gly | Ser | Asn | Val | Ser | Phe | Ser | Arg | Asp | Thr | Glu | Gly | Gly | Glu | Glu |
|     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| Glu | Pro | Ser | Lys | Thr | Gln | Pro | Gly | Met | Glu | Ser | Asp | Pro | Tyr | Glu | Ala |
|     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
| Glu | Asp | Phe | Val | Cys | Asp | Tyr | His | Leu | Glu | Met | Leu | Ser | Leu | Ser | Gln |
| 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |
| Asp | Gln | Gln | Asn | Pro | Ser | Cys | Ile | Gln | Phe | Asp | Asp | Ser | Asn | Trp | Gln |
|     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |

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Leu His Leu Thr Ser Leu Lys Pro Leu Gly Leu Asn Val Leu Leu Asn  
 580 585 590  
 Leu Cys Asp Ala Ser Val Thr Glu Arg Leu Cys Arg Phe Ser Asp His  
 595 600 605  
 Leu Cys Asn Ile Ala Leu Gln Glu Ser His Ser Ala Val Leu Pro Val  
 610 615 620  
 His Val Pro Trp Gly Leu Cys Glu Leu Ala Arg Leu Ile Gly Phe Thr  
 625 630 635 640  
 Pro Gly Ala Lys Glu Leu Phe Lys Gln Glu Asn His Leu Ala Leu Tyr  
 645 650 655  
 Arg Leu Pro Ser Ala Glu Thr Met Lys Glu Thr Ser Leu Gly Arg Leu  
 660 665 670  
 Ser Cys Val Thr Lys Arg Arg Pro Pro Leu Ser His Met Ile Ser Leu  
 675 680 685  
 Phe Ile Lys Asp Thr Thr Thr Ser Thr Glu Gln Met Leu Ser His Gly  
 690 695 700  
 Thr Ala Asp Val Val Leu Glu Ala Cys Thr Asp Phe Trp Asp Gly Ala  
 705 710 715 720  
 Asp Ile Tyr Pro Leu Ser Gly Ser Asp Arg Lys Lys Val Leu Asp Phe  
 725 730 735  
 Tyr Gln Arg Ala Cys Leu Ser Gly Tyr Cys Ser Ala Phe Ala Tyr Lys  
 740 745 750  
 Pro Met Asn Cys Ala Leu Ser Ser Gln Leu Asn Gly Lys Cys Ile Glu  
 755 760 765  
 Leu Val Gln Val Pro Gly Gln Ser Ser Ile Phe Thr Met Cys Glu Leu  
 770 775 780  
 Pro Ser Thr Ile Pro Ile Lys Gln Asn Ala Arg Arg Ser Ser Trp Ser  
 785 790 795 800  
 Ser Asp Glu Gly Ile Gly Glu Val Leu Glu Lys Glu Asp Cys Met Gln  
 805 810 815  
 Ala Leu Ser Gly Gln Ile Phe Met Gly Met Val Ser Ser Gln Tyr Gln  
 820 825 830  
 Ala Arg Leu Asp Ile Val Arg Leu Ile Asp Gly Leu Val Asn Ala Cys  
 835 840 845  
 Ile Arg Phe Val Tyr Phe Ser Leu Glu Asp Glu Leu Lys Ser Lys Val  
 850 855 860  
 Phe Ala Glu Lys Met Gly Leu Glu Thr Gly Trp Asn Cys His Ile Ser  
 865 870 875 880

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Leu Thr Pro Asn Gly Asp Met Pro Gly Ser Glu Ile Pro Pro Ser Ser  
 885 890 895  
 Pro Ser His Ala Gly Ser Leu His Asp Asp Leu Asn Gln Val Ser Arg  
 900 905 910  
 Asp Asp Ala Glu Gly Leu Leu Leu Met Glu Glu Glu Gly His Ser Asp  
 915 920 925  
 Leu Ile Ser Phe Gln Pro Thr Asp Ser Asp Ile Pro Ser Phe Leu Glu  
 930 935 940  
 Asp Ser Asn Arg Ala Lys Leu Pro Arg Gly Ile His Gln Val Arg Pro  
 945 950 955 960  
 His Leu Gln Asn Ile Asp Asn Val Pro Leu Leu Val Pro Leu Phe Thr  
 965 970 975  
 Asp Cys Thr Pro Glu Thr Met Cys Glu Met Ile Lys Ile Met Gln Glu  
 980 985 990  
 Tyr Gly Glu Val Thr Cys Cys Leu Gly Ser Ser Ala Asn Leu Arg Asn  
 995 1000 1005  
 Ser Cys Leu Phe Leu Gln Ser Asp Ile Ser Ile Ala Leu Asp Pro Leu  
 1010 1015 1020  
 Tyr Pro Ser Arg Cys Ser Trp Glu Thr Phe Gly Tyr Ala Thr Ser Ile  
 1025 1030 1035 1040  
 Ser Met Ala Gln Ala Ser Asp Gly Leu Ser Pro Leu Gln Leu Ser Gly  
 1045 1050 1055  
 Gln Leu Asn Ser Leu Pro Cys Ser Leu Thr Phe Arg Gln Glu Glu Thr  
 1060 1065 1070  
 Ile Ser Ile Ile Arg Leu Ile Glu Gln Ala Arg His Ala Thr Tyr Gly  
 1075 1080 1085  
 Ile Arg Lys Cys Phe Leu Phe Leu Leu Gln Cys Gln Leu Thr Leu Val  
 1090 1095 1100  
 Val Ile Gln Phe Leu Ser Cys Leu Val Gln Leu Pro Pro Leu Leu Ser  
 1105 1110 1115 1120  
 Thr Thr Asp Ile Leu Trp Leu Ser Cys Phe Cys Tyr Pro Leu Leu Ser  
 1125 1130 1135  
 Ile Ser Leu Leu Gly Lys Pro Pro His Ser Ser Ile Met Ser Met Ala  
 1140 1145 1150  
 Thr Gly Lys Asn Leu Gln Ser Ile Pro Lys Lys Thr Gln His Tyr Phe  
 1155 1160 1165  
 Leu Leu Cys Phe Leu Leu Lys Phe Ser Leu Thr Ile Ser Ser Cys Leu  
 1170 1175 1180

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Ile Cys Phe Gly Phe Thr Leu Gln Ser Phe Cys Asp Ser Ser Arg Asp  
 1185 1190 1195 1200

Arg Asn Leu Thr Asn Cys Ser Ser Val Met Leu Pro Ser Asn Asp Asp  
 1205 1210 1215

Arg Ala Pro Ala Trp Phe Glu Asp Phe Ala Asn Gly Leu Leu Ser Ala  
 1220 1225 1230

Gln Lys Leu Thr Ala Ala Leu Ile Val Leu His Thr Val Phe Ile Ser  
 1235 1240 1245

Ile Thr His Val His Arg Thr Lys Pro Leu Trp Arg Lys Ser Pro Leu  
 1250 1255 1260

Thr Asn Leu Trp Trp Ala Val Thr Val Pro Val Val Leu Leu Gly Gln  
 1265 1270 1275 1280

Val Val Gln Thr Ala Val Asp Leu Gln Leu Trp Thr His Arg Asp Ser  
 1285 1290 1295

His Val His Phe Gly Leu Glu Asp Val Pro Leu Leu Thr Trp Leu Leu  
 1300 1305 1310

Gly Cys Leu Ser Leu Val Leu Val Val Val Thr Asn Glu Ile Val Lys  
 1315 1320 1325

Leu His Glu Ile Arg Val Arg Val Arg Tyr Gln Lys Arg Gln Lys Leu  
 1330 1335 1340

Gln Phe Glu Thr Lys Leu Gly Met Asn Ser Pro Phe  
 1345 1350 1355

&lt;210&gt; 102

&lt;211&gt; 2030

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 102

```

tggctggcaa tggccttgc t gacctcgagc cgggcccacg tggggacott tggagcacag 60
cctacgatcc tgggtgcaagg ccggtggatg cagaggccag tccatatacc acccaggcct 120
gcgaggagcg tgggtcccccac ccattccagcc catatgtgca agtgcccttg acagagaggc 180
tgggtcatatc catggtgacc atttatgggc cacaacaggt ccccatctgc gcagtgaacc 240
ctgtgctgag caccttgacg acgtgatctt gcttcgtcct gcagcactgt gcggggcagg 300
aaaatccaag aggaagaagg atctacggat atcctgcatg tccaagccac ccgcacccaa 360
ccccacaccc ccccggaacc tggactcccg gaccttcac accattggag acagaaactt 420
tgagggtggag gctgatgact tggtgaccat ctgagaactg ggccgtggag cctatggggg 480
ggtagagaag gtgcggcacg ccagagcgcg caccatcatg gccgtgaagc ggatccgggc 540
caccgtgaac tcacaggagc agaagcggct gctcatggac ctggacatca acatgcgcac 600
ggtcgactgt ttctacactg tcaccttcta cggggcacta ttcagagagg gagacgtgtg 660
gatctgcatg gagctcatgg acacatcctt ggacaagttc taccggaagg tgctggataa 720
aaacatgaca attccagagg acatccttgg ggagattgct gtgtctatcg tgcgggccct 780
ggagcatctg cacagcaagc tgtcgggtgat ccacagagat gtgaagccct ccaatgtcct 840
tatcaacaag gagggccatg tgaagatgtg tgactttggc atcagtggct acttgggtgga 900
ctctgtggcc aagacgatgg atgcccgtg caagccctac atggcccctg agaggatcaa 960
cccagagctg aaccagaagg gctacaatgt caagtccgac gtctggagcc tgggcatcac 1020
catgattgag atggccatcc tgcgggttccc ttacgagtcc tgggggaccc cgttccagca 1080

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```

gctgaagcag gtggtggagg agccgtcccc ccagctcccc gccgaccgtt tctcccccca 1140
gtttgtggac ttcactgctc agtgcctgag gaagaacccc gcagagcgta tgagctacct 1200
ggagctgatg gagcaccctt tcttcacctt gcacaaaacc aagaagacgg acattgctgc 1260
cttcgtgaag aagatcctgg gagaagactc ataggggctg ggccctcggac cccactccgg 1320
ccctccagag cccacacagc ccatctgcgg gggcagtgtc caccacacac ataagctact 1380
gccatcctgg ccagggcat ctgggaggaa ccgagggggc tgctcccacc tggctctgtg 1440
gcgagccatt tgtcccaagt gccaaagaag cagaccattg gggctcccag ccaggccctt 1500
gtcggcccca ccagtgcctc tccctgctgc tcctaggacc cgtctccagc tgctgagatc 1560
ctggactgag ggggcctgga tgccccctgt ggatgctgct gcccctgcac agcaggctgc 1620
cagtgcctgg gtggatgggc caccgccttg cccagcctgg atgccatcca agttgtatat 1680
ttttttaatc tctcgactga atggactttg cacactttgg cccaggggtg ccacacctct 1740
atcccggtt tgggtgcggg tacacaagag gggatgagtt gtgtgaatac ccaagactc 1800
ccatgaggga gatgccatga gccgcccaag gccttcccc ggcaactggca aacagggcct 1860
ctgcggagca cactggctca cccagtcctg cccgccaccg ttatcgggtg cattcacctt 1920
tcgtgttttt ttttaatttat cctctgttga ttttttcttt tgcttttatg gtttggcttg 1980
tttttcttgc atggttttga gctgatcgct tctccccac cccctagggg 2030

```

&lt;210&gt; 103

&lt;211&gt; 318

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 103

```

Met Ser Lys Pro Pro Ala Pro Asn Pro Thr Pro Pro Arg Asn Leu Asp
 1          5          10          15

Ser Arg Thr Phe Ile Thr Ile Gly Asp Arg Asn Phe Glu Val Glu Ala
      20          25          30

Asp Asp Leu Val Thr Ile Ser Glu Leu Gly Arg Gly Ala Tyr Gly Val
      35          40          45

Val Glu Lys Val Arg His Ala Gln Ser Gly Thr Ile Met Ala Val Lys
      50          55          60

Arg Ile Arg Ala Thr Val Asn Ser Gln Glu Gln Lys Arg Leu Leu Met
      65          70          75          80

Asp Leu Asp Ile Asn Met Arg Thr Val Asp Cys Phe Tyr Thr Val Thr
      85          90          95

Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Val Trp Ile Cys Met Glu
      100          105          110

Leu Met Asp Thr Ser Leu Asp Lys Phe Tyr Arg Lys Val Leu Asp Lys
      115          120          125

Asn Met Thr Ile Pro Glu Asp Ile Leu Gly Glu Ile Ala Val Ser Ile
      130          135          140

Val Arg Ala Leu Glu His Leu His Ser Lys Leu Ser Val Ile His Arg
      145          150          155          160

Asp Val Lys Pro Ser Asn Val Leu Ile Asn Lys Glu Gly His Val Lys
      165          170          175

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Met Cys Asp Phe Gly Ile Ser Gly Tyr Leu Val Asp Ser Val Ala Lys  
 180 185 190

Thr Met Asp Ala Gly Cys Lys Pro Tyr Met Ala Pro Glu Arg Ile Asn  
 195 200 205

Pro Glu Leu Asn Gln Lys Gly Tyr Asn Val Lys Ser Asp Val Trp Ser  
 210 215 220

Leu Gly Ile Thr Met Ile Glu Met Ala Ile Leu Arg Phe Pro Tyr Glu  
 225 230 235 240

Ser Trp Gly Thr Pro Phe Gln Gln Leu Lys Gln Val Val Glu Glu Pro  
 245 250 255

Ser Pro Gln Leu Pro Ala Asp Arg Phe Ser Pro Glu Phe Val Asp Phe  
 260 265 270

Thr Ala Gln Cys Leu Arg Lys Asn Pro Ala Glu Arg Met Ser Tyr Leu  
 275 280 285

Glu Leu Met Glu His Pro Phe Phe Thr Leu His Lys Thr Lys Lys Thr  
 290 295 300

Asp Ile Ala Ala Phe Val Lys Lys Ile Leu Gly Glu Asp Ser  
 305 310 315

&lt;210&gt; 104

&lt;211&gt; 1648

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 104

```

atgcgggaga tcgtgcacat ccaggccggc cagtgcggca accagatcgg ggccaagtcc 60
tgggaagtca tcagtgatga gcatggcatc gaccccagcg gcaactacgt gggcgactcg 120
gacttgacgc tggagcggat cagcgtctac tacaacgagg cctcttctca caagtacgtg 180
cctcgagcca ttctggtgga cctggaaccc ggaaccatgg acagtgtccg ctgaggggcc 240
tttggacatc tcttcaggcc tgacaatttc atctttggtc agagtggggc cggcaacaac 300
tgggccaagg gtcactacac ggagggggcg gagctggtgg attcggtcct ggatgtggtg 360
cggaaggagt gtgaaaactg cgactgcctg cagggtctcc agctgaccca ctcgctgggg 420
ggggggacgg gctccggcat gggcacgttg ctcatcagca aggtgcgtga ggagtatccc 480
gaccgcatca tgaacacctt cagcgtcgtg ccctcaccca aggtgtcaga cacggtggtg 540
gaaccctaca acgccacgct gtccatccac cagctggtgg aaaacacgga tgaaacctac 600
tgcacgcaca acgaggcgct ctacgacatc tgcttccgca ccctcaagct ggccacgccc 660
acctacgggg acctcaacca cctggtatcg gccaccatga gcggagtcac cacctccttg 720
cgcttcccgg gccagctcaa cgctgacctg cgcaagctgg ccgtcaacat ggtgcccttc 780
ccgcgcctgc acttcttcat gcccgcttc gcccccctca ccaggcgggg cagccagcag 840
taccggggcc tgaccgtgcc cgagctcacc cagcagatgt tcgatgccaa gaacatgatg 900
gccgcctgcg acccgcgcca cggcgctac ctgacggtgg ccaccgtgtt ccggggccgc 960
atgtccatga aggaggtgga cgagcagatg ctggccatcc agagcaagaa cagcagctac 1020
ttcgtggagt ggatccccaa caacgtgaag gtggccgtgt gtgacatccc gcccgcggc 1080
ctcaagatgt cctccacctt catcggaac agcacggcca tccaggagct gttcaagcgc 1140
atctccgagc agttcacggc catgttccgg cgcaaggcct tcctgcaact gtacacgggc 1200
gagggcatgg acgagatgga gttcacccag gccgagagca acatgaacga cctggtgtcc 1260
gagtaccagc agtaccagga cgccacggcc gaggaagagg gcgagatgta cgaagacgac 1320
gaggaggagt cggaggccca gggccccaag tgaaactgct gcgagctgga gtgagaggca 1380
ggtggcggcc ggggccaag ccagcagtgt ctaaaccctt ggagccatct tgctgcccac 1440

```

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```

accctgcttt ccccatcgcc ctagggctcc cttgccgccc tctgcagta tttatggcct 1500
cgctctcccc cacctaggcc acgtgtgagc tgctcctgtc tctgtcttat tgcagctcca 1560
ggcctgacgt tttacgggtt tgttttttac tggtttgtgt ttatatatttc ggggatactt 1620
aataaatcta ttgctgtcag ataccctt 1648

```

&lt;210&gt; 105

&lt;211&gt; 450

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 105

```

Met Arg Glu Ile Val His Ile Gln Ala Gly Gln Cys Gly Asn Gln Ile
  1             5             10             15

```

```

Gly Ala Lys Phe Trp Glu Val Ile Ser Asp Glu His Gly Ile Asp Pro
      20             25             30

```

```

Ser Gly Asn Tyr Val Gly Asp Ser Asp Leu Gln Leu Glu Arg Ile Ser
      35             40             45

```

```

Val Tyr Tyr Asn Glu Ala Ser Ser His Lys Tyr Val Pro Arg Ala Ile
      50             55             60

```

```

Leu Val Asp Leu Glu Pro Gly Thr Met Asp Ser Val Arg Ser Gly Ala
      65             70             75             80

```

```

Phe Gly His Leu Phe Arg Pro Asp Asn Phe Ile Phe Gly Gln Ser Gly
      85             90             95

```

```

Ala Gly Asn Asn Trp Ala Lys Gly His Tyr Thr Glu Gly Ala Glu Leu
      100            105            110

```

```

Val Asp Ser Val Leu Asp Val Val Arg Lys Glu Cys Glu Asn Cys Asp
      115            120            125

```

```

Cys Leu Gln Gly Phe Gln Leu Thr His Ser Leu Gly Gly Gly Thr Gly
      130            135            140

```

```

Ser Gly Met Gly Thr Leu Leu Ile Ser Lys Val Arg Glu Glu Tyr Pro
      145            150            155            160

```

```

Asp Arg Ile Met Asn Thr Phe Ser Val Val Pro Ser Pro Lys Val Ser
      165            170            175

```

```

Asp Thr Val Val Glu Pro Tyr Asn Ala Thr Leu Ser Ile His Gln Leu
      180            185            190

```

```

Val Glu Asn Thr Asp Glu Thr Tyr Cys Ile Asp Asn Glu Ala Leu Tyr
      195            200            205

```

```

Asp Ile Cys Phe Arg Thr Leu Lys Leu Ala Thr Pro Thr Tyr Gly Asp
      210            215            220

```

```

Leu Asn His Leu Val Ser Ala Thr Met Ser Gly Val Thr Thr Ser Leu
      225            230            235            240

```



|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Arg | Phe | Pro | Gly | Gln | Leu | Asn | Ala | Asp | Leu | Arg | Lys | Leu | Ala | Val | Asn |  |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |  |
| Met | Val | Pro | Phe | Pro | Arg | Leu | His | Phe | Phe | Met | Pro | Gly | Phe | Ala | Pro |  |
|     |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |  |
| Leu | Thr | Arg | Arg | Gly | Ser | Gln | Gln | Tyr | Arg | Ala | Leu | Thr | Val | Pro | Glu |  |
|     |     |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |  |
| Leu | Thr | Gln | Gln | Met | Phe | Asp | Ala | Lys | Asn | Met | Met | Ala | Ala | Cys | Asp |  |
|     |     |     |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |  |
| Pro | Arg | His | Gly | Arg | Tyr | Leu | Thr | Val | Ala | Thr | Val | Phe | Arg | Gly | Arg |  |
|     |     |     |     | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |  |
| Met | Ser | Met | Lys | Glu | Val | Asp | Glu | Gln | Met | Leu | Ala | Ile | Gln | Ser | Lys |  |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |
| Asn | Ser | Ser | Tyr | Phe | Val | Glu | Trp | Ile | Pro | Asn | Asn | Val | Lys | Val | Ala |  |
|     |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |  |
| Val | Cys | Asp | Ile | Pro | Pro | Arg | Gly | Leu | Lys | Met | Ser | Ser | Thr | Phe | Ile |  |
|     |     |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |  |
| Gly | Asn | Ser | Thr | Ala | Ile | Gln | Glu | Leu | Phe | Lys | Arg | Ile | Ser | Glu | Gln |  |
|     |     |     |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |  |
| Phe | Thr | Ala | Met | Phe | Arg | Arg | Lys | Ala | Phe | Leu | His | Trp | Tyr | Thr | Gly |  |
|     |     |     |     | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |  |
| Glu | Gly | Met | Asp | Glu | Met | Glu | Phe | Thr | Glu | Ala | Glu | Ser | Asn | Met | Asn |  |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |  |
| Asp | Leu | Val | Ser | Glu | Tyr | Gln | Gln | Tyr | Gln | Asp | Ala | Thr | Ala | Glu | Glu |  |
|     |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |  |
| Glu | Gly | Glu | Met | Tyr | Glu | Asp | Asp | Glu | Glu | Glu | Ser | Glu | Ala | Gln | Gly |  |
|     |     |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |  |
| Pro | Lys |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|     |     |     |     | 450 |     |     |     |     |     |     |     |     |     |     |     |  |

```
<210> 106
<211> 1633
<212> DNA
<213> Homo sapiens
```

| <400> 106   |             |             |            |            |             |     |  |
|-------------|-------------|-------------|------------|------------|-------------|-----|--|
| cagaatctcc  | ggcagttttt  | gtacctcaag  | aagtaagtgg | aacacctttc | cctgtcatag  | 60  |  |
| ttattttcat  | ccagacatct  | ggtggaagca  | tcagattcct | tacagatata | agagagggcat | 120 |  |
| cattttaaaag | gtagaacagg  | atcgacaaac  | aaggatttat | gtcaggatct | ctcagcctct  | 180 |  |
| gtgttaccga  | gggcattttct | aacagtcttc  | ttactacggc | ctcgcgcgac | cgcgcgctcg  | 240 |  |
| ccccgccgct  | cctgctgcag  | ccccagggcc  | cctcgccgcc | gccaccatgg | acgccatcaa  | 300 |  |
| gaagaagatg  | catagtgctga | agctcgacaa  | ggagaacgcc | ttggatcgag | ctgagcaggc  | 360 |  |
| ggaggccgac  | aagaagcgcg  | cggaagacag  | gagcaagcag | ctggaatcg  | agctggtgtc  | 420 |  |
| actgcaaaag  | aaactcaagg  | gcaccgaaga  | tgaactggac | aaatactctg | aggtctcaa   | 480 |  |
| agatgcccgag | gagaagctgg  | agctggcgaga | gaaaaaggcc | accqatgctg | aaqccgacgt  | 540 |  |

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agcttctctg aacagacgca tccagctggt tgaggaagag ttggatcgtg cccaggagcg 600
tctggcaaca gctttgcaga agctggagga agctgagaag gcagcagatg agagtgcagag 660
aggcatgaaa gtcattgaga gtcgagccca aaaagatgaa gaaaaaatgg aaattcagga 720
gatccaactg aaagaggcaa agcacattgc tgaagatgcc gaccgcaaat atgaagaggt 780
ggcccgtaa gctggtcatca ttgagagcga cctggaacgt gcagaggagc gggctgagct 840
ctcagaaggc caagtccgac agctggaaga acaattaaga ataatggatc agaccttgaa 900
agcattaatg gctgcagagg ataagtactc gcagaaggaa gacagatatg aggaagagat 960
caaggtcctt tccgacaagc tgaaggaggc tgagactcgg gctgagtttg cggagagggtc 1020
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agaaaacctt agtatgcac agatgctgga tcagacttta ctggagttaa acaacatgtg 1140
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cacctgctta ccccttaaat gcaattttatt tacttttacc actgtcacag aaacatccac 1260
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gcgatcctgg ttcaaagtgt ccatttcccc gggtgatgct gccacacttt gtagagagtt 1380
tagcaacaca gtgtgcttag tcagcgtagg aatcctcact aaagcaggag aagttccatt 1440
caaagtgcca atgatagagt caacaaggaa ggtaaatgtt ggaaacacaa tcaggtgtgg 1500
attggtgcta ctttgaacaa aaggtcccc tgtggtcttt tgttcaacat tgtacaatgt 1560
agaactctgt ccaacactaa tttattttgt cttgagtttt actacaagat gagactatgt 1620
atcccgcattg cct 1633

```

&lt;210&gt; 107

&lt;211&gt; 284

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 107

```

Met Asp Ala Ile Lys Lys Lys Met Gln Met Leu Lys Leu Asp Lys Glu
  1             5             10             15

```

```

Asn Ala Leu Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala
      20             25             30

```

```

Glu Asp Arg Ser Lys Gln Leu Glu Asp Glu Leu Val Ser Leu Gln Lys
  35             40             45

```

```

Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu
  50             55             60

```

```

Lys Asp Ala Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp
  65             70             75             80

```

```

Ala Glu Ala Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu
      85             90             95

```

```

Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys
  100             105             110

```

```

Leu Glu Glu Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys
  115             120             125

```

```

Val Ile Glu Ser Arg Ala Gln Lys Asp Glu Glu Lys Met Glu Ile Gln
  130             135             140

```

```

Glu Ile Gln Leu Lys Glu Ala Lys His Ile Ala Glu Asp Ala Asp Arg
  145             150             155             160

```

|            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Lys        | Tyr        | Glu        | Glu        | Val<br>165 | Ala        | Arg        | Lys        | Leu        | Val<br>170 | Ile        | Ile        | Glu        | Ser        | Asp<br>175 | Leu        |
| Glu        | Arg        | Ala        | Glu<br>180 | Glu        | Arg        | Ala        | Glu        | Leu<br>185 | Ser        | Glu        | Gly        | Gln        | Val<br>190 | Arg        | Gln        |
| Leu        | Glu        | Glu<br>195 | Gln        | Leu        | Arg        | Ile        | Met<br>200 | Asp        | Gln        | Thr        | Leu        | Lys<br>205 | Ala        | Leu        | Met        |
| Ala        | Ala<br>210 | Glu        | Asp        | Lys        | Tyr        | Ser<br>215 | Gln        | Lys        | Glu        | Asp        | Arg<br>220 | Tyr        | Glu        | Glu        | Glu        |
| Ile<br>225 | Lys        | Val        | Leu        | Ser        | Asp<br>230 | Lys        | Leu        | Lys        | Glu        | Ala<br>235 | Glu        | Thr        | Arg        | Ala        | Glu<br>240 |
| Phe        | Ala        | Glu        | Arg        | Ser<br>245 | Val        | Thr        | Lys        | Leu        | Glu<br>250 | Lys        | Ser        | Ile        | Asp        | Asp<br>255 | Leu        |
| Glu        | Glu        | Lys        | Val<br>260 | Ala        | His        | Ala        | Lys        | Glu<br>265 | Glu        | Asn        | Leu        | Ser        | Met<br>270 | His        | Gln        |
| Met        | Leu        | Asp<br>275 | Gln        | Thr        | Leu        | Leu        | Glu<br>280 | Leu        | Asn        | Asn        | Met        |            |            |            |            |

| <400> 108  |             |            |            |             |            |      |
|------------|-------------|------------|------------|-------------|------------|------|
| ttacacttta | tacttccggc  | tcgaaatttg | tgtggaattg | tgancggata  | acaatttcac | 60   |
| acaggaaaca | nctatgacct  | tgattacgcc | aagctcgaaa | ttaaccctca  | ctaaagggaa | 120  |
| caaaagctgg | agctcgcgcg  | cctgcaggtc | gacactagtg | gatccaaaga  | attcggcacg | 180  |
| aggcgacggg | cggagcggag  | cgcggcgcgc | cggggccgcc | gccgggggga  | tcggctgcct | 240  |
| ccccggggcg | ggtgtagaga  | gggcgggtcc | ccggcctcgg | gagcacggcg  | gtggagggga | 300  |
| cataggaggc | ggccatggcg  | acccccggca | acctagggtc | ctccgtcctg  | gcgagcaaga | 360  |
| ccaagaccaa | gaagaagcac  | ttcgtagcgc | agaaagtga  | gctgtttcgg  | gccagcgacc | 420  |
| cgctgctcag | cgtcctcatg  | tggggggtaa | accactcgat | caatgaactg  | agccatgttc | 480  |
| aaatccctgt | tatgttgatg  | ccagatgact | tcaaagccta | ttcaaaaata  | aaggtggaca | 540  |
| atcacctttt | taacaaagaa  | aacatgccga | gccatttcaa | gtttaaggaa  | tactgcccg  | 600  |
| tggctctccg | taactgcggg  | aagaggtttg | gaattgatgt | tcaagatttc  | cagaattccc | 660  |
| tgaccaggag | cgcacccctc  | cccaacgact | cccaggcccc | cagtggagct  | cgttttcaca | 720  |
| cttcctacga | caaaagatac  | atgatcaaga | ctattaccag | tgaagacgtg  | gccgaaatgc | 780  |
| acaacatcct | gaagaataac  | caccagtaca | tagtggaaat | tcatgggatc  | acccttcttc | 840  |
| cccacttggt | gggcattgtac | cggcttaatg | ttgatggagt | tgaatatatat | gtgatagtta | 900  |
| caagaaatgt | attcagccac  | cgtttgctct | tgtataggaa | atacgactta  | aagggtctta | 960  |
| cagtggctag | agaagctagt  | gacaaagaaa | aggccaaaga | actgccaaact | ctgaaagata | 1020 |

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```

atgatttcat taatgagggc caaaagattt atattgatga caacagcaag aaggtcttcc 1080
tggaact aaaaaggat gttgagtttc tggccagct gaagctcatg gactacagtc 1140
tgctggtggg aattcatgat gtggagagag ccgaacagga ggaagtggag tgtgaggaga 1200
acgatgggga ggaggagggc gagagcgatg gcacccaccc ggtgggaacc ccccagata 1260
gccccgggaa tacactgaac agctcaccac ccctggctcc cggggagttc gagccgaaca 1320
tcgacgtcta tggaattaag tgccatgaaa actcgcctag gaaggaggtg tacttcatgg 1380
caattattga catccttact cattatgatg caaaaaagaa agctgcccac gctgcaaaaa 1440
ctgttaaaca tggcgctggc gcggagatct ccaccgtgaa cccagaacag tattcaaagc 1500
gctttttgga ctttattggc cacatcttga cgtaacctcc tgcgcayctc ggacagcatg 1560
aacattggat ggacagaggt ggcttcggtg taggaaaaat gaaaaccaa ctcagtgaag 1620
tactcatctt gcaggaagca aacctccttg tttacatctt caggccaaga tgactgattt 1680
gggggctact cgctttacag ctacctgatt ttcccagcat cgttctagct atttctgact 1740
ttgtgtatat gtgtgtgtgt gtgtgttggg ggggggtgag tgtgtgcccg cgtgtgcatt 1800
taaagcataa attaattaaa cagccacttc ggtca 1835

```

&lt;210&gt; 109

&lt;211&gt; 406

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 109

```

Met Ala Thr Pro Gly Asn Leu Gly Ser Ser Val Leu Ala Ser Lys Thr
  1             5             10             15

Lys Thr Lys Lys Lys His Phe Val Ala Gln Lys Val Lys Leu Phe Arg
          20             25             30

Ala Ser Asp Pro Leu Leu Ser Val Leu Met Trp Gly Val Asn His Ser
          35             40             45

Ile Asn Glu Leu Ser His Val Gln Ile Pro Val Met Leu Met Pro Asp
          50             55             60

Asp Phe Lys Ala Tyr Ser Lys Ile Lys Val Asp Asn His Leu Phe Asn
          65             70             75             80

Lys Glu Asn Met Pro Ser His Phe Lys Phe Lys Glu Tyr Cys Pro Met
          85             90             95

Val Phe Arg Asn Cys Gly Lys Arg Phe Gly Ile Asp Val Gln Asp Phe
          100            105            110

Gln Asn Ser Leu Thr Arg Ser Ala Pro Leu Pro Asn Asp Ser Gln Ala
          115            120            125

Arg Ser Gly Ala Arg Phe His Thr Ser Tyr Asp Lys Arg Tyr Met Ile
          130            135            140

Lys Thr Ile Thr Ser Glu Asp Val Ala Glu Met His Asn Ile Leu Lys
          145            150            155            160

Lys Tyr His Gln Tyr Ile Val Glu Cys His Gly Ile Thr Leu Leu Pro
          165            170            175

His Leu Leu Gly Met Tyr Arg Leu Asn Val Asp Gly Val Glu Ile Tyr
          180            185            190

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Val Ile Val Thr Arg Asn Val Phe Ser His Arg Leu Ser Val Tyr Arg  
 195 200 205

Lys Tyr Asp Leu Lys Gly Ser Thr Val Ala Arg Glu Ala Ser Asp Lys  
 210 215 220

Glu Lys Ala Lys Glu Leu Pro Thr Leu Lys Asp Asn Asp Phe Ile Asn  
 225 230 235 240

Glu Gly Gln Lys Ile Tyr Ile Asp Asp Asn Ser Lys Lys Val Phe Leu  
 245 250 255

Glu Lys Leu Lys Lys Asp Val Glu Phe Leu Ala Gln Leu Lys Leu Met  
 260 265 270

Asp Tyr Ser Leu Leu Val Gly Ile His Asp Val Glu Arg Ala Glu Gln  
 275 280 285

Glu Glu Val Glu Cys Glu Glu Asn Asp Gly Glu Glu Glu Gly Glu Ser  
 290 295 300

Asp Gly Thr His Pro Val Gly Thr Pro Pro Asp Ser Pro Gly Asn Thr  
 305 310 315 320

Leu Asn Ser Ser Pro Pro Leu Ala Pro Gly Glu Phe Glu Pro Asn Ile  
 325 330 335

Asp Val Tyr Gly Ile Lys Cys His Glu Asn Ser Pro Arg Lys Glu Val  
 340 345 350

Tyr Phe Met Ala Ile Ile Asp Ile Leu Thr His Tyr Asp Ala Lys Lys  
 355 360 365

Lys Ala Ala His Ala Ala Lys Thr Val Lys His Gly Ala Gly Ala Glu  
 370 375 380

Ile Ser Thr Val Asn Pro Glu Gln Tyr Ser Lys Arg Phe Leu Asp Phe  
 385 390 395 400

Ile Gly His Ile Leu Thr  
 405

&lt;210&gt; 110

&lt;211&gt; 2572

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 110

```

aacagaatta gttggcccag ctctgcctat aagtagctga atgtcttgag gcaacttcaa 60
cgtttccttg gaccttagat tccttgccctg taaaacagca tggggccaga tgatctctaa 120
gggtccttct ggctctgaag gcaatgatct ggggcatgga acctgtagtt agagagctgg 180
gaaatgggca gatgtgggct ccagggcacc cagaattgca ggcttaggag ctaacagcaa 240
ccaggattct gtagtctagc aatcttgctt tacaggtagg gaaactgggc ctagaaaggc 300
gaagtgattt ttttgccctc ctcagcttta ttctctttt cctctgaact gtagagtcta 360
aagattcagc acaaagcagt tttgtgtagt ggatacataa gcttttttgt tgttattttt 420
ctgaattatt ttgttgactt tcaaagtttt ttttacataa acagtaaattg ctcgttataa 480
aaatttccat taatacagga agtgaaaaaa gtaaaaaact gcaaattgct gttatcctcc 540

```

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```

cacccttacc ccctaggtcc ccagaggtgt ctctgttaac agttcagcgt gtatccatcc 600
tgactcctcc aataaatgca gaaacttgta tgtctctccc cgacaactgg attatcatat 660
acattattca agcataggct ttagactcag acatatctac atctaataccc agcttatagc 720
taattatttg agtgaccttg gccaaagtgt tcatccagtt ttagtctcaa tctccccatg 780
tgtaaaatga aaataataat agtatctacc tggcctggcg tggcggtta tgcctataat 840
cccagccctt tggaagaccg aggctagtgg atcccttgag ctccaggagt caagaccaac 900
ctgggcaatt tagcaagacc tcatctctac tgaaaaacaa aaaacaaaaa aactccccca 960
aaattagcca agtgtgctgg tgtgcacctg tagtcccagc tactcggaag gctgaggtgg 1020
gagaatcgct tgagccagga aagacgaggc tgcagtgagc tgtgattgca ccaactgcact 1080
gcaacctgag caacagagcg ataccttggt tctgttaaaa caaacaacaa aacaaaatag 1140
tatctacctt ataggatcat ggtgaagatt taatgagatt ttatatgaat agcacttaac 1200
agttcctggt actgatatga gtaagcacta cacacacaca cacacacaca 1260
cacacagagc acagaatgag ttagaggtaa agtgaaaact aaaccccaag ttttctgacc 1320
ctcagttctc tcgactttct accacatctc tctgcttctc tcctaggtgc ctaggcatgg 1380
gttcagtgct cactacttgt tgaatgaatg actgaggttg tgtgtaaggg ggtagatcta 1440
gggatctgag gtctgtggag ttccctgggat gcctgctctg gaaaatggag gctttcatcc 1500
tgtgagttgg gaggggtgtg ggcagtggtg gttggctgga ccagctggtg cttcagagct 1560
ccatgcctgg agagttgggc ctctaggcag agctgagggc ccagagtggc tctcagctta 1620
aaggatcttg gcttagaagg aatgtgcagt gggctgcctc tgctcgggag gggctaaaaa 1680
aagcctcacc ctcccctggg ctttgtgtga ggcttatcaa ctgctcaagt cagctcatct 1740
ctctggctgc tccggcatat ttgagaaggt ctgtttccct ggtccttctg gggttccacc 1800
aattggcaag aagggatcag cctgtcctag aggtgaagag agagctgtgg catgaagggg 1860
agggggctgg tggcccaaaa cctggtgaca atacacagtt gtcagctgta ccctgctggc 1920
gtttcttctt tttatagtca gcagcagttg ctcttgcttt caccagccc ctctgtgggg 1980
ctcctgcccc ggataaaagg gaagggaggc agcccaggct cctatctcat ctcccagacg 2040
ccacgtctct cggtttcttc ttagatcact cctctgccaa agatcccaac aagacaacat 2100
ggctcccaag aagcctgagc ctaagaagga ggcagccaag ccagctccag ctccagctcc 2160
agccctgca ccagccctg cccagctcc tgaggctccc aaggaacctg cctttgaccc 2220
caagagtgtg aaggtaaagt aggtcagcc attgggatag aggtgggat gacattgaga 2280
gtccttttgc tctggagctt agcgatctac tttatgtggg ctggactggg atgaggacta 2340
gggtgtccat gccccagatc gcagtcccat ggggcagtgg agtgggtgtt ggggctgatg 2400
agggggagat tgagtcataa accttttccg tcaagaatga ggtgctgctt tgagggagcc 2460
ctgtcctgct accctagatt tgtgcagcta agttgggaat ggggggaggt acaaccaacc 2520
atccatccac ccttttataa ggcattaatg aggaccacca tagcaaagta aa 2572

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&lt;210&gt; 111

&lt;211&gt; 197

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 111

```

Met Ala Pro Lys Lys Pro Glu Pro Lys Lys Glu Ala Ala Lys Pro Ala
  1                      5                      10                      15

```

```

Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Glu
      20                      25                      30

```

```

Ala Pro Lys Glu Pro Ala Phe Asp Pro Lys Ser Val Lys Ile Asp Phe
      35                      40                      45

```

```

Thr Ala Asp Gln Ile Glu Glu Phe Lys Glu Ala Phe Ser Leu Phe Asp
      50                      55                      60

```

```

Arg Thr Pro Thr Gly Glu Met Lys Ile Thr Tyr Gly Gln Cys Gly Asp
      65                      70                      75                      80

```

<400> 113  
Met Lys Val Glu Val Leu Pro Ala Leu Thr Asp Asn Tyr Met Tyr Leu  
1 5 10 15

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Val Ile Asp Asp Glu Thr Lys Glu Ala Ala Ile Val Asp Pro Val Gln  
                   20                                  25                                  30  
 Pro Gln Lys Val Val Asp Ala Ala Arg Lys His Gly Val Lys Leu Thr  
                   35                                  40                                  45  
 Thr Val Leu Thr Thr His His His Trp Asp His Ala Gly Gly Asn Glu  
           50                                  55                                  60  
 Lys Leu Val Lys Leu Glu Ser Gly Leu Lys Val Tyr Gly Gly Asp Asp  
   65                                  70                                  75                                  80  
 Arg Ile Gly Ala Leu Thr His Lys Ile Thr His Leu Ser Thr Leu Gln  
                                   85                                  90                                  95  
 Val Gly Ser Leu Asn Val Lys Cys Leu Ala Thr Pro Cys His Thr Ser  
                   100                                  105                                  110  
 Gly His Ile Cys Tyr Phe Val Ser Lys Pro Gly Gly Ser Glu Pro Pro  
   115                                  120                                  125  
 Ala Val Phe Thr Gly Asp Thr Leu Phe Val Ala Gly Cys Gly Lys Phe  
   130                                  135                                  140  
 Tyr Glu Gly Thr Ala Asp Glu Met Cys Lys Ala Leu Leu Glu Val Leu  
  145                                  150                                  155                                  160  
 Gly Arg Leu Pro Pro Asp Thr Arg Val Tyr Cys Gly His Glu Tyr Thr  
                   165                                  170                                  175  
 Ile Asn Asn Leu Lys Phe Ala Arg His Val Glu Pro Gly Asn Ala Ala  
                   180                                  185                                  190  
 Ile Arg Glu Lys Leu Ala Trp Ala Lys Glu Lys Tyr Ser Ile Gly Glu  
   195                                  200                                  205  
 Pro Thr Val Pro Ser Thr Leu Ala Glu Glu Phe Thr Tyr Asn Pro Phe  
   210                                  215                                  220  
 Met Arg Val Arg Glu Lys Thr Val Gln Gln His Ala Gly Glu Thr Asp  
  225                                  230                                  235                                  240  
 Pro Val Thr Thr Met Arg Ala Val Arg Arg Glu Lys Asp Gln Phe Lys  
                   245                                  250                                  255  
 Met Pro Arg Asp  
                   260

&lt;210&gt; 114

&lt;211&gt; 2233

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 114

agagggggccc cgcgcgcgga tctcgcgaga gcattagagg gcggaagcgc tatccgagca 60  
 ggatgcgggtt cgtggttgcc ttggctctcc tgaacgtcgc agcggcgagg gccgtgccgc 120



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```

tcttgccac cgaaagcgtc aagcaagaag aagctggagt acggccttct gcaggaaacg 180
tctccacca cccagacttg agccaacggc ctggaggctc taccaagtcg catccggagc 240
cgcagactcc aaaagacagc cctagcaagt cgagtgcgga ggcgcagacc ccagaagaca 300
cccccaaca gtccgggtggg gaggcaaaga ccctaaaaga cagctccaac aagtcgggtg 360
cggaggcaca gacccccaaa ggcagcacta gcaagtcggg ttcggaggcg cagaccacaa 420
aagacagcac tagtaagtcg catccggagc tgcagactcc aaaagacagc actggcfaat 480
cgggtgcgga ggcgcagacc ccagaagaca gccccaacag gtcgggtgcg gagccaaaga 540
cccaaaaaga cagccctagc aagtcagggt cggaggcgca gaccacaaaa gatgtcccta 600
ataagtcggg tgcggacggc cagaccccaa aagacggctc cagcaagtcg ggtgcggagg 660
atcagacccc aaaagacgtc cctaacaagt cgggtgcgga gaagcagact ccaaaagacg 720
gctctaaca gtccggtgca gaggagcagg gcccaataga cgggcccagc aagtcgggtg 780
cggaggagca gacctcaaaa gacagcccta acaagggtgt tccagagcag cctcccga 840
aagaccattc caagcccatc tccaaccctt ctgataacaa ggagctcccc aaggctgaca 900
caaaccagct tgctgacaaa gggaagcttt ctctcatgc tttcaaaacc gaatctgggg 960
aggaaactga cctcatttct ccccgcagg aggaagttaa gtcttcagag cctactgagg 1020
atgtggggcc caaagaggct gaagatgatg atacaggacc cgaggagggc tcaccgcccc 1080
aagaagagaa agaaaagatg tccggttctg cctccagtga gaaccgtgaa gggacacttt 1140
cggattccac gggtagcgag aaggatgacc tttatccgaa cggttctgga aatggcagcg 1200
cggagagcag ccacttcttt gcatactctg tgactgcagc cattcttggt gctgtcctct 1260
atatcgctca tcacaacaag cggaagatca ttgcttttgt cctggaagga aaaagatcta 1320
aagtcacccg gcggccaaag gccagtgact accaacgttt ggaccagaag atcttttctc 1380
ccccagctcc taacagaatg gtatatctct ctggaaaaag atgaacgtca ccaatggatt 1440
gtgctgctct cgtttcagct ttgatttttt tgtccttgag aaccttggtc tccctgctga 1500
tttgtttcta aatcaaaaga aatgaagaaa aaagtactgt gacctgagag acacctctct 1560
ctagaattta gtggcgggtc tgggctggca gaggtagggg gctgctttgg gctttgcacc 1620
tgcacttttg tgacattgtt cttctgtgtt ccctttattt atgctggtgg cttccatccg 1680
ttctcctctg gggtagtggt aggggtatat ggaaacacgg ctatgaccaa agggagatcc 1740
cagcctgggc agcctgcgct gctgaccacc ctccctgggg cccgggctct gtaggaaagt 1800
tggtccttga ctgtggcatt gcactctgca ctgtttctct ctgcagacct aggggaaaac 1860
tgagggtgga agtgcttttc tactaaggcc tcttactttg ggggggatgt gccctacaga 1920
agacatagaa gatggggaaa tgccaatggg caaagagcta ctttgaatac ataattctct 1980
tcaaagactt cagcagcaaa cctaaacagc aggttaaaaa aaaagatgct tttttgggtg 2040
caagtctaac ctgtctagca tgagatcttc ttgattttct gattatttta ttagcttga 2100
gacaaagtga atcaacttcc acttagttgt accgagcata aaacagaact tgggcttctc 2160
ggcagtgagg ccactgtccc atcacagatt tttaaaataa atatgatttg aagtagtgtg 2220
atctttcaca caa 2233

```

&lt;210&gt; 115

&lt;211&gt; 453

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 115

```

Met Arg Phe Val Val Ala Leu Val Leu Leu Asn Val Ala Ala Ala Gly
  1             5             10             15

```

```

Ala Val Pro Leu Leu Ala Thr Glu Ser Val Lys Gln Glu Glu Ala Gly
          20             25             30

```

```

Val Arg Pro Ser Ala Gly Asn Val Ser Thr His Pro Ser Leu Ser Gln
          35             40             45

```

```

Arg Pro Gly Gly Ser Thr Lys Ser His Pro Glu Pro Gln Thr Pro Lys
          50             55             60

```

```

Asp Ser Pro Ser Lys Ser Ser Ala Glu Ala Gln Thr Pro Glu Asp Thr
          65             70             75             80

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|            |     |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
|------------|-----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Pro        | Asn | Lys        | Ser        | Gly<br>85  | Gly        | Glu        | Ala        | Lys        | Thr<br>90  | Leu        | Lys        | Asp        | Ser        | Ser<br>95  | Asn        |
| Lys        | Ser | Gly        | Ala<br>100 | Glu        | Ala        | Gln        | Thr        | Pro<br>105 | Lys        | Gly        | Ser        | Thr        | Ser<br>110 | Lys        | Ser        |
| Gly        | Ser | Glu        | Ala<br>115 | Gln        | Thr        | Thr        | Lys<br>120 | Asp        | Ser        | Thr        | Ser        | Lys<br>125 | Ser        | His        | Pro        |
| Glu        | Leu | Gln        | Thr        | Pro        | Lys        | Asp<br>135 | Ser        | Thr        | Gly        | Lys        | Ser<br>140 | Gly        | Ala        | Glu        | Ala        |
| Gln<br>145 | Thr | Pro        | Glu        | Asp<br>150 | Ser        | Pro        | Asn        | Arg        | Ser        | Gly<br>155 | Ala        | Glu        | Pro        | Lys        | Thr<br>160 |
| Gln        | Lys | Asp        | Ser        | Pro<br>165 | Ser        | Lys        | Ser        | Gly        | Ser<br>170 | Glu        | Ala        | Gln        | Thr        | Thr<br>175 | Lys        |
| Asp        | Val | Pro        | Asn<br>180 | Lys        | Ser        | Gly        | Ala        | Asp<br>185 | Gly        | Gln        | Thr        | Pro        | Lys<br>190 | Asp        | Gly        |
| Ser        | Ser | Lys<br>195 | Ser        | Gly        | Ala        | Glu        | Asp<br>200 | Gln        | Thr        | Pro        | Lys        | Asp<br>205 | Val        | Pro        | Asn        |
| Lys<br>210 | Ser | Gly        | Ala        | Glu        | Lys        | Gln<br>215 | Thr        | Pro        | Lys        | Asp        | Gly<br>220 | Ser        | Asn        | Lys        | Ser        |
| Gly<br>225 | Ala | Glu        | Glu        | Gln        | Gly<br>230 | Pro        | Ile        | Asp        | Gly        | Pro<br>235 | Ser        | Lys        | Ser        | Gly        | Ala<br>240 |
| Glu        | Glu | Gln        | Thr        | Ser<br>245 | Lys        | Asp        | Ser        | Pro        | Asn<br>250 | Lys        | Val        | Val        | Pro        | Glu<br>255 | Gln        |
| Pro        | Ser | Arg        | Lys<br>260 | Asp        | His        | Ser        | Lys        | Pro<br>265 | Ile        | Ser        | Asn        | Pro        | Ser<br>270 | Asp        | Asn        |
| Lys        | Glu | Leu<br>275 | Pro        | Lys        | Ala        | Asp        | Thr<br>280 | Asn        | Gln        | Leu        | Ala        | Asp<br>285 | Lys        | Gly        | Lys        |
| Leu<br>290 | Ser | Pro        | His        | Ala        | Phe        | Lys<br>295 | Thr        | Glu        | Ser        | Gly        | Glu<br>300 | Glu        | Thr        | Asp        | Leu        |
| Ile<br>305 | Ser | Pro        | Pro        | Gln        | Glu<br>310 | Glu        | Val        | Lys        | Ser        | Ser<br>315 | Glu        | Pro        | Thr        | Glu        | Asp<br>320 |
| Val        | Gly | Pro        | Lys        | Glu<br>325 | Ala        | Glu        | Asp        | Asp<br>330 | Asp        | Thr        | Gly        | Pro        | Glu<br>335 | Glu        | Gly        |
| Ser        | Pro | Pro        | Lys<br>340 | Glu        | Glu        | Lys        | Glu        | Lys<br>345 | Met        | Ser        | Gly        | Ser        | Ala<br>350 | Ser        | Ser        |
| Glu        | Asn | Arg<br>355 | Glu        | Gly        | Thr        | Leu        | Ser<br>360 | Asp        | Ser        | Thr        | Gly        | Ser<br>365 | Glu        | Lys        | Asp        |
| Asp<br>370 | Leu | Tyr        | Pro        | Asn        | Gly<br>375 | Ser        | Gly        | Asn        | Gly        | Ser        | Ala<br>380 | Glu        | Ser        | Ser        | His        |

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Phe Phe Ala Tyr Leu Val Thr Ala Ala Ile Leu Val Ala Val Leu Tyr  
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 Lys Arg Ser Lys Val Thr Arg Arg Pro Lys Ala Ser Asp Tyr Gln Arg  
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 <213> Homo sapiens

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 ctctctctaag gccatgggaa tcatgaactc cttcgtcaac gacatcttcg aacgcatcgc 240  
 ggggtgaggct tcccgcctgg cgcattacaa caagcgctcg accatcacct ccagggagat 300  
 ccagacggcc gtgcgcctgc tgctgcccgg ggagttggcc aagcacgccc tgctccgaggg 360  
 caccaaggcc gtcaccaagt acaccagcgc taagtaaaact tgccaaggag ggactttctc 420  
 tggaatttcc tgatatgacc aagaaagctt cttatcaaaa gaagcacaat tgccttcggt 480  
 tacctcatta tctactgcag aaaagaagac gagaatgcaa ccatacctag atggactttt 540  
 ccacaagcta aagctggcct cttgatctca ttcagattcc aaagagaatc atttacaagt 600  
 taatttctgt ctcttggtc cattccttct ctttaataat catttactgt tcctcaaaga 660  
 attgtttaca ttacccatct cctcttttgc tctgagaaag agtatataag cttctgtacc 720  
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 <213> Homo sapiens

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 35 40 45  
 Val His Pro Asp Thr Gly Ile Ser Ser Lys Ala Met Gly Ile Met Asn  
 50 55 60  
 Ser Phe Val Asn Asp Ile Phe Glu Arg Ile Ala Gly Glu Ala Ser Arg  
 65 70 75 80

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Ala | His | Tyr | Asn | Lys | Arg | Ser | Thr | Ile | Thr | Ser | Arg | Glu | Ile | Gln |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| Thr | Ala | Val | Arg | Leu | Leu | Leu | Pro | Gly | Glu | Leu | Ala | Lys | His | Ala | Val |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Ser | Glu | Gly | Thr | Lys | Ala | Val | Thr | Lys | Tyr | Thr | Ser | Ala | Lys |     |     |
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| cgggagctga  | ggcgaggct  | ggccagagcg | tggagaggaa  | agccctttcc  | atcctcaagg | 120  |
| ccgttgccagg | agatgccgc  | gagccacctt | cgccagcacc  | acaccggggt  | gtaatggata | 180  |
| ggtaacagag  | aagacctcgt | cccttcctag | tcaggggcatc | agcatgactg  | agtgtcttct | 240  |
| gccccccacc  | agcagcccca | gtgaacaccg | caggggtggag | catggcagcg  | ggcttaccgc | 300  |
| gacccccagc  | tctgaagaga | tcagccctac | taagttttct  | ggattgtacc  | gcactggcga | 360  |
| gccttcacct  | ccccatgaca | tcttcctatg | gcctctctgt  | gtagtgtctg  | atgatgagaa | 420  |
| agatcatggg  | aagaaaaaag | ggaaatttaa | gaaaaaggaa  | aagaggactg  | aaggctatgc | 480  |
| agcctttcag  | gaagatagct | ctggagatga | ggcagaaagt  | ccttctaaaa  | tgaagaggtc | 540  |
| caagggaatc  | catgttttca | agaagccag  | cttttctaaa  | aagaaggaaa  | aggattttaa | 600  |
| aataaaagag  | aaacccaaag | aagaaaagca | taaagaagaa  | aagcaciaag  | aagaaaaaca | 660  |
| taaagagaag  | aagtcaaaag | acttgacagc | agctgatgtt  | gttaaacagt  | ggaaggaaaa | 720  |
| gaagaaaaag  | aaaaagccaa | ttcaggagcc | agaggtgcct  | cagattgatg  | ttccaaatct | 780  |
| caaaccatt   | tttggaattc | ctttggctga | tgcagtagag  | aggaccatga  | tgtatgatgg | 840  |
| cattcggtcg  | ccagccgttt | tcogtgaatg | tatagattac  | gtagagaagt  | atggcatgaa | 900  |
| gtgtgaaggc  | atctacagag | tatcaggaat | taaatcaaag  | gtggatgagc  | taaaagcagc | 960  |
| ctatgaccgg  | gaggagtcta | caaacttgga | agactatgag  | cctaacactg  | tagccagttt | 1020 |
| gctgaagcag  | tatttgcgag | accttcagag | gaatttgctt  | accaagagac  | ttatgccagg | 1080 |
| atttgaagag  | gcttgtggga | ggaccacgga | gactgagaaa  | gtgcaggaat  | tccagcgttt | 1140 |
| actcaaagaa  | ctgccagaat | gtaactatct | tctgatttct  | tggctcattg  | tgcacatgga | 1200 |
| ccatgtcatt  | gcaaaggaac | tggaaacaaa | aatgaatata  | cagaacattt  | ctatagtgtc | 1260 |
| cagcccaact  | gtgcagatca | gcaatcgagt | cctgtatgtg  | tttttcacac  | atgtgcaaga | 1320 |
| actcttttga  | aatgtggtac | taaagcaagt | gatgaaacct  | ctgcgatgg   | ctaactatgg | 1380 |
| cacgatgcc   | acgctgccag | agaccaggg  | gggcatcaag  | gaggagatca  | ggagacagga | 1440 |
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| catgatgata  | ctgactgaac | aggaggagct | cctggccatg  | gagcagtttc  | tgccgaggga | 1740 |
| gattgcctca  | gaaaaagaag | agattgaacg | cctcagagct  | gagattgctg  | aaattcagag | 1800 |
| tcgccagcag  | cacggccgaa | gtgagactga | ggagtactcc  | tccgagagcg  | agagcgagag | 1860 |
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| tgagccaaaa  | gcagctaaag | agcagccaaa | ggcaggcaag  | gagccggcaa  | agccatcgcc | 2160 |
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| agactggaag  | gacccgtgca | tcttactgta | acccgggggc  | caggccggct  | ctctcgctgt | 2280 |
| acattctgta  | aagggttctt | ctcttctcag | actcttctct  | tgtcacacgt  | ctgactcctt | 2340 |
| cacgtcaggc  | tcaggttcca | tgggaggacg | aagcagtgga  | cgcatttgtg  | gctttaggga | 2400 |
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&lt;211&gt; 655

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 119

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Ile Ser Pro Thr Lys Phe Pro Gly Leu Tyr Arg Thr Gly Glu Pro Ser
          35                               40                               45

Pro Pro His Asp Ile Leu His Glu Pro Pro Asp Val Val Ser Asp Asp
          50                               55                               60

Glu Lys Asp His Gly Lys Lys Lys Gly Lys Phe Lys Lys Lys Glu Lys
          65                               70                               75                               80

Arg Thr Glu Gly Tyr Ala Ala Phe Gln Glu Asp Ser Ser Gly Asp Glu
          85                               90                               95

Ala Glu Ser Pro Ser Lys Met Lys Arg Ser Lys Gly Ile His Val Phe
          100                               105                               110

Lys Lys Pro Ser Phe Ser Lys Lys Lys Glu Lys Asp Phe Lys Ile Lys
          115                               120                               125

Glu Lys Pro Lys Glu Glu Lys His Lys Glu Glu Lys His Lys Glu Glu
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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
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| Lys | His | Lys | Glu | Lys | Lys | Ser | Lys | Asp | Leu | Thr | Ala | Ala | Asp | Val | Val | 145 | 150 | 155 | 160 |
| Lys | Gln | Trp | Lys | Glu | Lys | Lys | Lys | Lys | Lys | Lys | Pro | Ile | Gln | Glu | Pro | 165 | 170 | 175 |     |
| Glu | Val | Pro | Gln | Ile | Asp | Val | Pro | Asn | Leu | Lys | Pro | Ile | Phe | Gly | Ile | 180 | 185 | 190 |     |
| Pro | Leu | Ala | Asp | Ala | Val | Glu | Arg | Thr | Met | Met | Tyr | Asp | Gly | Ile | Arg | 195 | 200 | 205 |     |
| Leu | Pro | Ala | Val | Phe | Arg | Glu | Cys | Ile | Asp | Tyr | Val | Glu | Lys | Tyr | Gly | 210 | 215 | 220 |     |
| Met | Lys | Cys | Glu | Gly | Ile | Tyr | Arg | Val | Ser | Gly | Ile | Lys | Ser | Lys | Val | 225 | 230 | 235 | 240 |
| Asp | Glu | Leu | Lys | Ala | Ala | Tyr | Asp | Arg | Glu | Glu | Ser | Thr | Asn | Leu | Glu | 245 | 250 | 255 |     |
| Asp | Tyr | Glu | Pro | Asn | Thr | Val | Ala | Ser | Leu | Leu | Lys | Gln | Tyr | Leu | Arg | 260 | 265 | 270 |     |
| Asp | Leu | Pro | Glu | Asn | Leu | Leu | Thr | Lys | Glu | Leu | Met | Pro | Arg | Phe | Glu | 275 | 280 | 285 |     |
| Glu | Ala | Cys | Gly | Arg | Thr | Thr | Glu | Thr | Glu | Lys | Val | Gln | Glu | Phe | Gln | 290 | 295 | 300 |     |
| Arg | Leu | Leu | Lys | Glu | Leu | Pro | Glu | Cys | Asn | Tyr | Leu | Leu | Ile | Ser | Trp | 305 | 310 | 315 | 320 |
| Leu | Ile | Val | His | Met | Asp | His | Val | Ile | Ala | Lys | Glu | Leu | Glu | Thr | Lys | 325 | 330 | 335 |     |
| Met | Asn | Ile | Gln | Asn | Ile | Ser | Ile | Val | Leu | Ser | Pro | Thr | Val | Gln | Ile | 340 | 345 | 350 |     |
| Ser | Asn | Arg | Val | Leu | Tyr | Val | Phe | Phe | Thr | His | Val | Gln | Glu | Leu | Phe | 355 | 360 | 365 |     |
| Gly | Asn | Val | Val | Leu | Lys | Gln | Val | Met | Lys | Pro | Leu | Arg | Trp | Ser | Asn | 370 | 375 | 380 |     |
| Met | Ala | Thr | Met | Pro | Thr | Leu | Pro | Glu | Thr | Gln | Ala | Gly | Ile | Lys | Glu | 385 | 390 | 395 | 400 |
| Glu | Ile | Arg | Arg | Gln | Glu | Phe | Leu | Leu | Asn | Cys | Leu | His | Arg | Asp | Leu | 405 | 410 | 415 |     |
| Gln | Gly | Gly | Ile | Lys | Asp | Leu | Ser | Lys | Glu | Glu | Arg | Leu | Trp | Glu | Val | 420 | 425 | 430 |     |
| Gln | Arg | Ile | Leu | Thr | Ala | Leu | Lys | Arg | Lys | Leu | Arg | Glu | Ala | Lys | Arg | 435 | 440 | 445 |     |

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Gln Glu Cys Glu Thr Lys Ile Ala Gln Glu Ile Ala Ser Leu Ser Lys  
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 485 490 495  
 Leu Ala Met Glu Gln Phe Leu Arg Arg Gln Ile Ala Ser Glu Lys Glu  
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 Glu Ile Glu Arg Leu Arg Ala Glu Ile Ala Glu Ile Gln Ser Arg Gln  
 515 520 525  
 Gln His Gly Arg Ser Glu Thr Glu Glu Tyr Ser Ser Glu Ser Glu Ser  
 530 535 540  
 Glu Ser Glu Asp Glu Glu Glu Leu Gln Ile Ile Leu Glu Asp Leu Gln  
 545 550 555 560  
 Arg Gln Asn Glu Glu Leu Glu Ile Lys Asn Asn His Leu Asn Gln Ala  
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&lt;211&gt; 746

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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87/147

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<222> (654)..(654)  
<223> n is a, c, g, or t

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<222> (657)..(658)  
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<222> (666)..(668)  
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<223> n is a, c, g, or t

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<223> n is a, c, g, or t

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 aagaatgnat tgctgagggg agacctgggc cagggtcttc tccctgttaa tccagggcca 120  
 cactgatgag ntctgggggn tctgcacaca cccctcccag aaccgnttcc tcacctgcgg 180  
 ccacgaccgg nagttctgcc tgtgggatgg ggagagccat gcactggcct ggagcatcga 240  
 cctcaaggag actggtctct gtgctgactt ccacccgagt ggggcagttg tggccgnagg 300  
 actgaacacg gggaggtggt tgggttttgn cacagagacc agagagatcg tgtctgatgt 360  
 cattgatggc aatnagcagc tctcagtggc caatcttttn gnggtttcca ggggatgggt 420  
 ccaattggtt ccccatnaca acntnatntt caatcttttn gnggtttcca ggggatgggt 480  
 cccaattcca gncnttttgg ggccntttgt ntttgggtca acnccagnt tcaaccactc 540  
 aatnttggag taggttcaan nnttngnntt accagttggn nttntccaan nnnnnnnnnn 600  
 nntntnnntt nnttnttctt ttncntnann cnnnnnnnnn nncnnntctn cntnttnttc 660  
 aancnnttn nnnnnncnnn cnnnnncntn tnnctnctn nnnncnntnn nntnntnnn 720  
 cnnnnnctnn nnntnnncnn nnnnnn 746

<210> 121  
 <211> 1211  
 <212> DNA  
 <213> Homo sapiens

<400> 121  
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 ggcacggtag ttccgcccggg tctggcttcc gcctgccgag cgcccccgga ccgcaggccg 180  
 gactacactt cccgtcggcc cgcctgctct cccgatgccg ccttggcgcg agacgttggc 240  
 aagcagagt tctccaagat ggccgcttgg ggaaggaggc gtcttgccc gggcagcagt 300  
 ggcggcagcg cccgagagag ggtgagcttg tcggccacag actgctacat tgtgcatgag 360

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atctacaatg gggagaatgc ccaagaccag tttgagtacg agctggagca ggccctggaa 420
gccagtaga agtacattgt gattgagccc actcgcatg gcgacgagac agcccgtctg 480
atcacctgg gcaactgcct gcacaagacg gccgtgctgg cgggcaccgc ctgcctcttc 540
accccgcttg cgctgccctt agattattcc cactacattt ccctgccgcg tgggtgtgctg 600
agcctggcct gctgcaccct ctatgggatc tcctggcagt ttgacccttg ctgcaagtac 660
caagtggagt acgacgccta taaactgtcg cgctgcctc tgcacacact cacctcctcc 720
accccgctgg tgctggtccg gaaggacgac ctgcacagaa agagactgca caacacgata 780
gcactggccg ccctggtgta ctgtgtaaag aagatttacg aactctatgc cgtatgattt 840
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tcgccacact ctgtgaggca gcagagcctg ggcaggtgtt tggcttagta tttgttattt 960
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atttcaactc c                                     1211

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&lt;210&gt; 122

&lt;211&gt; 192

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 122

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Met Ala Ala Trp Gly Arg Arg Arg Leu Gly Pro Gly Ser Ser Gly Gly
  1             5             10             15

Ser Ala Arg Glu Arg Val Ser Leu Ser Ala Thr Asp Cys Tyr Ile Val
      20             25             30

His Glu Ile Tyr Asn Gly Glu Asn Ala Gln Asp Gln Phe Glu Tyr Glu
    35             40             45

Leu Glu Gln Ala Leu Glu Ala Gln Tyr Lys Tyr Ile Val Ile Glu Pro
    50             55             60

Thr Arg Ile Gly Asp Glu Thr Ala Arg Trp Ile Thr Val Gly Asn Cys
    65             70             75             80

Leu His Lys Thr Ala Val Leu Ala Gly Thr Ala Cys Leu Phe Thr Pro
      85             90             95

Leu Ala Leu Pro Leu Asp Tyr Ser His Tyr Ile Ser Leu Pro Ala Gly
    100             105             110

Val Leu Ser Leu Ala Cys Cys Thr Leu Tyr Gly Ile Ser Trp Gln Phe
    115             120             125

Asp Pro Cys Cys Lys Tyr Gln Val Glu Tyr Asp Ala Tyr Lys Leu Ser
    130             135             140

Arg Leu Pro Leu His Thr Leu Thr Ser Ser Thr Pro Val Val Leu Val
    145             150             155             160

Arg Lys Asp Asp Leu His Arg Lys Arg Leu His Asn Thr Ile Ala Leu
      165             170             175

Ala Ala Leu Val Tyr Cys Val Lys Lys Ile Tyr Glu Leu Tyr Ala Val
    180             185             190

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<210> 123  
 <211> 1568  
 <212> DNA  
 <213> Homo sapiens

<400> 123  
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 agcgagcccc ggccgcccgcg accaccagcc gcgctaaccg ccgaccaacc gccaccgagg 180  
 cgcctgagcg agagcagagg aggaggaggc atgagtgagg cgggcgaggc caccaccacc 240  
 accaccacca ccctcccgca ggctccgacg gaggcggccg ccgcgggtcc ccaggacccc 300  
 gcgccaaga gcccggtggg cagcggtgcg ccccaggccg cggccccggc gcccgccgcc 360  
 cacgtcgag gaaacccccg tggggacgag gccctgag ccacgggcac cgcggccgcc 420  
 gcctctttag ccgcccgcgc cggcagcgaa gacgcggaga aaaaagtctt cgccacccaa 480  
 gtccttgga ctgtcaaagt gttcaacgtc agaaatggat atggatttat aaatcgaaat 540  
 gacaccaaag aagatgtatt tgtacatcag actgccatca agaagaataa ccacggaaa 600  
 tatctgcgca gtgtaggaga tggagaaact gtagagtttg atgtggttga aggagagaag 660  
 ggtgcagaag ctgccaatgt gactggcccg gatggagttc ctgtggaagg gagtgcgttac 720  
 gctgcagatc ggcgccgtta cagacgtggc tactatggaa ggcgccgttg cctccccgg 780  
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 gccactgata ggcagttctc tggggcccgg aatcagctgc gccgccccca gtatcgccct 900  
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 taccgtagca ggggacctcc tcgccacga cctgccccag cagttggaga ggctgaagat 1140  
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 cgtccctaca attaccggcg tcgccgcgcg tcctcctaac gtccttcac aagatggcaa 1260  
 agaggccaag gcaggtgaag caccaactga gaacctgct ccaccaccc agcagagcag 1320  
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 catccaagca ataaagtga agactaacca agatttggac attggaatgt ttactgttat 1500  
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<210> 124  
 <211> 412  
 <212> PRT  
 <213> Homo sapiens

<400> 124  
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 20 25 30  
 Glu Ile Arg Pro Gly Leu Pro Glu Ser Glu Pro Arg Pro Arg Pro  
 35 40 45  
 Pro Ala Ala Leu Thr Ala Asp Gln Pro Pro Pro Arg Arg Leu Ser Glu  
 50 55 60

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Ser Arg Gly Gly Gly Gly Met Ser Glu Ala Gly Glu Ala Thr Thr Thr  
 65 70 75 80  
 Thr Thr Thr Thr Leu Pro Gln Ala Pro Thr Glu Ala Ala Ala Ala Ala  
 85 90 95  
 Pro Gln Asp Pro Ala Pro Lys Ser Pro Val Gly Ser Gly Ala Pro Gln  
 100 105 110  
 Ala Ala Ala Pro Ala Pro Ala Ala His Val Ala Gly Asn Pro Gly Gly  
 115 120 125  
 Asp Ala Ala Pro Ala Ala Thr Gly Thr Ala Ala Ala Ala Ser Leu Ala  
 130 135 140  
 Ala Ala Ala Gly Ser Glu Asp Ala Glu Lys Lys Val Leu Ala Thr Lys  
 145 150 155 160  
 Val Leu Gly Thr Val Lys Trp Phe Asn Val Arg Asn Gly Tyr Gly Phe  
 165 170 175  
 Ile Asn Arg Asn Asp Thr Lys Glu Asp Val Phe Val His Gln Thr Ala  
 180 185 190  
 Ile Lys Lys Asn Asn Pro Arg Lys Tyr Leu Arg Ser Val Gly Asp Gly  
 195 200 205  
 Glu Thr Val Glu Phe Asp Val Val Glu Gly Glu Lys Gly Ala Glu Ala  
 210 215 220  
 Ala Asn Val Thr Gly Pro Asp Gly Val Pro Val Glu Gly Ser Arg Tyr  
 225 230 235 240  
 Ala Ala Asp Arg Arg Arg Tyr Arg Arg Gly Tyr Tyr Gly Arg Arg Arg  
 245 250 255  
 Gly Pro Pro Arg Asn Tyr Ala Gly Glu Glu Glu Glu Gly Ser Gly  
 260 265 270  
 Ser Ser Glu Gly Phe Asp Pro Pro Ala Thr Asp Arg Gln Phe Ser Gly  
 275 280 285  
 Ala Arg Asn Gln Leu Arg Arg Pro Gln Tyr Arg Pro Gln Tyr Arg Gln  
 290 295 300  
 Arg Arg Phe Pro Pro Tyr His Val Gly Gln Thr Phe Asp Arg Arg Ser  
 305 310 315 320  
 Arg Val Leu Pro His Pro Asn Arg Ile Gln Ala Gly Glu Ile Gly Glu  
 325 330 335  
 Met Lys Asp Gly Val Pro Glu Gly Ala Gln Leu Gln Gly Pro Val His  
 340 345 350  
 Arg Asn Pro Thr Tyr Arg Pro Arg Tyr Arg Ser Arg Gly Pro Pro Arg  
 355 360 365



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Pro Arg Pro Ala Pro Ala Val Gly Glu Ala Glu Asp Lys Glu Asn Gln  
 370 375 380

Gln Ala Thr Ser Gly Pro Asn Gln Pro Ser Val Arg Arg Gly Tyr Arg  
 385 390 395 400

Arg Pro Tyr Asn Tyr Arg Arg Arg Pro Pro Ser Ser  
 405 410

&lt;210&gt; 125

&lt;211&gt; 2963

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 125

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aagaatggca tcgacatcta cagcctcacc gtggactcca ggggtctcatc ccgatttgcc 180
cacacggtcg tcaccagccg agtggtcaat agggccaata cggtagacga ggccaccttc 240
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&lt;210&gt; 126

&lt;211&gt; 930

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 126

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Met Lys Pro Pro Arg Pro Val Arg Thr Cys Ser Lys Val Leu Val Leu
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Leu Ser Leu Leu Ala Ile His Gln Thr Thr Thr Ala Glu Lys Asn Gly
      20                               25                               30

Ile Asp Ile Tyr Ser Leu Thr Val Asp Ser Arg Val Ser Ser Arg Phe
      35                               40                               45

Ala His Thr Val Val Thr Ser Arg Val Val Asn Arg Ala Asn Thr Val
      50                               55                               60

Gln Glu Ala Thr Phe Gln Met Glu Leu Pro Lys Lys Ala Phe Ile Thr
      65                               70                               75                               80

Asn Phe Ser Met Asn Ile Asp Gly Met Thr Tyr Pro Gly Ile Ile Lys
      85                               90                               95

Glu Lys Ala Glu Ala Gln Ala Gln Tyr Ser Ala Ala Val Ala Lys Gly
      100                               105                               110

Lys Asn Ala Gly Leu Val Lys Ala Thr Gly Arg Asn Met Glu Gln Phe
      115                               120                               125

Gln Val Ser Val Ser Val Ala Pro Asn Ala Lys Ile Thr Phe Glu Leu
      130                               135                               140

Val Tyr Glu Glu Leu Leu Lys Arg Arg Leu Gly Val Tyr Glu Leu Leu
      145                               150                               155                               160

Leu Lys Val Arg Pro Gln Gln Leu Val Lys His Leu Gln Met Asp Ile
      165                               170                               175

His Ile Phe Glu Pro Gln Gly Ile Ser Phe Leu Glu Thr Glu Ser Thr
      180                               185                               190

Phe Met Thr Asn Gln Leu Val Asp Ala Leu Thr Thr Trp Gln Asn Lys
      195                               200                               205

Thr Lys Ala His Ile Arg Phe Lys Pro Thr Leu Ser Gln Gln Gln Lys
      210                               215                               220

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Pro | Glu | Gln | Gln | Glu | Thr | Val | Leu | Asp | Gly | Asn | Leu | Ile | Ile | Arg | 225 | 230 | 235 | 240 |
| Tyr | Asp | Val | Asp | Arg | Ala | Ile | Ser | Gly | Gly | Ser | Ile | Gln | Ile | Glu | Asn | 245 | 250 | 255 |     |
| Gly | Tyr | Phe | Val | His | Tyr | Phe | Ala | Pro | Glu | Gly | Leu | Thr | Thr | Met | Pro | 260 | 265 | 270 |     |
| Lys | Asn | Val | Val | Phe | Val | Ile | Asp | Lys | Ser | Gly | Ser | Met | Ser | Gly | Arg | 275 | 280 | 285 |     |
| Lys | Ile | Gln | Gln | Thr | Arg | Glu | Ala | Leu | Ile | Lys | Ile | Leu | Asp | Asp | Leu | 290 | 295 | 300 |     |
| Ser | Pro | Arg | Asp | Gln | Phe | Asn | Leu | Ile | Val | Phe | Ser | Thr | Glu | Ala | Thr | 305 | 310 | 315 | 320 |
| Gln | Trp | Arg | Pro | Ser | Leu | Val | Pro | Ala | Ser | Ala | Glu | Asn | Val | Asn | Lys | 325 | 330 | 335 |     |
| Ala | Arg | Ser | Phe | Ala | Ala | Gly | Ile | Gln | Ala | Leu | Gly | Gly | Thr | Asn | Ile | 340 | 345 | 350 |     |
| Asn | Asp | Ala | Met | Leu | Met | Ala | Val | Gln | Leu | Leu | Asp | Ser | Ser | Asn | Gln | 355 | 360 | 365 |     |
| Glu | Glu | Arg | Leu | Pro | Glu | Gly | Ser | Val | Ser | Leu | Ile | Ile | Leu | Leu | Thr | 370 | 375 | 380 |     |
| Asp | Gly | Asp | Pro | Thr | Val | Gly | Glu | Thr | Asn | Pro | Arg | Ser | Ile | Gln | Asn | 385 | 390 | 395 | 400 |
| Asn | Val | Arg | Glu | Ala | Val | Ser | Gly | Arg | Tyr | Ser | Leu | Phe | Cys | Leu | Gly | 405 | 410 | 415 |     |
| Phe | Gly | Phe | Asp | Val | Ser | Tyr | Ala | Phe | Leu | Glu | Lys | Leu | Ala | Leu | Asp | 420 | 425 | 430 |     |
| Asn | Gly | Gly | Leu | Ala | Arg | Arg | Ile | His | Glu | Asp | Ser | Asp | Ser | Ala | Leu | 435 | 440 | 445 |     |
| Gln | Leu | Gln | Asp | Phe | Tyr | Gln | Glu | Val | Ala | Asn | Pro | Leu | Leu | Thr | Ala | 450 | 455 | 460 |     |
| Val | Thr | Phe | Glu | Tyr | Pro | Ser | Asn | Ala | Val | Glu | Glu | Val | Thr | Gln | Asn | 465 | 470 | 475 | 480 |
| Asn | Phe | Arg | Leu | Leu | Phe | Lys | Gly | Ser | Glu | Met | Val | Val | Ala | Gly | Lys | 485 | 490 | 495 |     |
| Leu | Gln | Asp | Arg | Gly | Pro | Asp | Val | Leu | Thr | Ala | Thr | Val | Ser | Gly | Lys | 500 | 505 | 510 |     |
| Leu | Pro | Thr | Gln | Asn | Ile | Thr | Phe | Gln | Thr | Glu | Ser | Ser | Val | Ala | Glu | 515 | 520 | 525 |     |

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Glu | Ala | Glu | Phe | Gln | Ser | Pro | Lys | Tyr | Ile | Phe | His | Asn | Phe | Met |
| 530 |     |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
| Glu | Arg | Leu | Trp | Ala | Tyr | Leu | Thr | Ile | Gln | Gln | Leu | Leu | Glu | Gln | Thr |
| 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |
| Val | Ser | Ala | Ser | Asp | Ala | Asp | Gln | Gln | Ala | Leu | Arg | Asn | Gln | Ala | Leu |
|     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |
| Asn | Leu | Ser | Leu | Ala | Tyr | Ser | Phe | Val | Thr | Pro | Leu | Thr | Ser | Met | Val |
|     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |
| Val | Thr | Lys | Pro | Asp | Asp | Gln | Glu | Gln | Ser | Gln | Val | Ala | Glu | Lys | Pro |
|     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |
| Met | Glu | Gly | Glu | Ser | Arg | Asn | Arg | Asn | Val | His | Ser | Gly | Ser | Thr | Phe |
|     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |
| Phe | Lys | Tyr | Tyr | Leu | Gln | Gly | Ala | Lys | Ile | Pro | Lys | Pro | Glu | Ala | Ser |
| 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |
| Phe | Ser | Pro | Arg | Arg | Gly | Trp | Asn | Arg | Gln | Ala | Gly | Ala | Ala | Gly | Ser |
|     |     |     |     | 645 |     |     |     |     | 650 |     |     |     |     | 655 |     |
| Arg | Met | Asn | Phe | Arg | Pro | Gly | Val | Leu | Ser | Ser | Arg | Gln | Leu | Gly | Leu |
|     |     |     | 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |     |
| Pro | Gly | Pro | Pro | Asp | Val | Pro | Asp | His | Ala | Ala | Tyr | His | Pro | Phe | Arg |
|     |     | 675 |     |     |     |     | 680 |     |     |     |     | 685 |     |     |     |
| Arg | Leu | Ala | Ile | Leu | Pro | Ala | Ser | Ala | Pro | Pro | Ala | Thr | Ser | Asn | Pro |
|     | 690 |     |     |     |     | 695 |     |     |     |     | 700 |     |     |     |     |
| Asp | Pro | Ala | Val | Ser | Arg | Val | Met | Asn | Met | Lys | Ile | Glu | Glu | Thr | Thr |
| 705 |     |     |     |     | 710 |     |     |     |     | 715 |     |     |     |     | 720 |
| Met | Thr | Thr | Gln | Thr | Pro | Ala | Pro | Ile | Gln | Ala | Pro | Ser | Ala | Ile | Leu |
|     |     |     | 725 |     |     |     |     |     | 730 |     |     |     |     | 735 |     |
| Pro | Leu | Pro | Gly | Gln | Ser | Val | Glu | Arg | Leu | Cys | Val | Asp | Pro | Arg | His |
|     |     |     | 740 |     |     |     |     | 745 |     |     |     |     | 750 |     |     |
| Arg | Gln | Gly | Pro | Val | Asn | Leu | Leu | Ser | Asp | Pro | Glu | Gln | Gly | Val | Glu |
|     |     | 755 |     |     |     |     | 760 |     |     |     |     | 765 |     |     |     |
| Val | Thr | Gly | Gln | Tyr | Glu | Arg | Glu | Lys | Ala | Gly | Phe | Ser | Trp | Ile | Glu |
|     | 770 |     |     |     |     | 775 |     |     |     |     | 780 |     |     |     |     |
| Val | Thr | Phe | Lys | Asn | Pro | Leu | Val | Trp | Val | His | Ala | Ser | Pro | Glu | His |
|     | 785 |     |     |     | 790 |     |     |     |     | 795 |     |     |     |     | 800 |
| Val | Val | Val | Thr | Arg | Asn | Arg | Arg | Ser | Ser | Ala | Tyr | Lys | Trp | Lys | Glu |
|     |     |     |     | 805 |     |     |     |     | 810 |     |     |     |     | 815 |     |
| Thr | Leu | Phe | Ser | Val | Met | Pro | Gly | Leu | Lys | Met | Thr | Met | Asp | Lys | Thr |
|     |     |     | 820 |     |     |     |     | 825 |     |     |     |     | 830 |     |     |

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Gly Leu Leu Leu Leu Ser Asp Pro Asp Lys Val Thr Ile Gly Leu Leu  
 835 840 845  
 Phe Trp Asp Gly Arg Gly Glu Gly Leu Arg Leu Leu Leu Arg Asp Thr  
 850 855 860  
 Asp Arg Phe Ser Ser His Val Gly Gly Thr Leu Gly Gln Phe Tyr Gln  
 865 870 875 880  
 Glu Val Leu Trp Gly Ser Pro Ala Ala Ser Asp Asp Gly Arg Arg Thr  
 885 890 895  
 Leu Arg Val Gln Gly Asn Asp His Ser Ala Thr Arg Glu Arg Arg Leu  
 900 905 910  
 Asp Tyr Gln Glu Gly Pro Pro Gly Val Glu Ile Ser Cys Trp Ser Val  
 915 920 925  
 Glu Leu  
 930

<210> 127  
 <211> 191  
 <212> PRT  
 <213> Homo sapiens

<400> 127  
 Met Asn Phe Leu Leu Ser Trp Val His Trp Ser Leu Ala Leu Leu Leu  
 1 5 10 15  
 Tyr Leu His His Ala Lys Trp Ser Gln Ala Ala Pro Met Ala Glu Gly  
 20 25 30  
 Gly Gly Gln Asn His His Glu Val Val Lys Phe Met Asp Val Tyr Gln  
 35 40 45  
 Arg Ser Tyr Cys His Pro Ile Glu Thr Leu Val Asp Ile Phe Gln Glu  
 50 55 60  
 Tyr Pro Asp Glu Ile Glu Tyr Ile Phe Lys Pro Ser Cys Val Pro Leu  
 65 70 75 80  
 Met Arg Cys Gly Gly Cys Ser Asn Asp Glu Gly Leu Glu Cys Val Pro  
 85 90 95  
 Thr Glu Glu Ser Asn Ile Thr Met Gln Ile Met Arg Ile Lys Pro His  
 100 105 110  
 Gln Gly Gln His Ile Gly Glu Met Ser Phe Leu Gln His Asn Lys Cys  
 115 120 125  
 Glu Cys Arg Pro Lys Lys Asp Arg Ala Arg Gln Glu Asn Pro Cys Gly  
 130 135 140  
 Pro Cys Ser Glu Arg Arg Lys His Leu Phe Val Gln Asp Pro Gln Thr  
 145 150 155 160

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Cys Lys Cys Ser Cys Lys Asn Thr His Ser Arg Cys Lys Ala Arg Gln  
                           165                          170                          175

Leu Glu Leu Asn Glu Arg Thr Cys Arg Cys Asp Lys Pro Arg Arg  
                           180                          185                          190

&lt;210&gt; 128

&lt;211&gt; 221

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 128

Met Pro Val Met Arg Leu Phe Pro Cys Phe Leu Gln Leu Leu Ala Gly  
   1                          5                          10                          15

Leu Ala Leu Pro Ala Val Pro Pro Gln Gln Trp Ala Leu Ser Ala Gly  
                           20                          25                          30

Asn Gly Ser Ser Glu Val Glu Val Val Pro Phe Gln Glu Val Trp Gly  
                           35                          40                          45

Arg Ser Tyr Cys Arg Ala Leu Glu Arg Leu Val Asp Val Val Ser Glu  
                           50                          55                          60

Tyr Pro Ser Glu Val Glu His Met Phe Ser Pro Ser Cys Val Ser Leu  
   65                          70                          75                          80

Leu Arg Cys Thr Gly Cys Cys Gly Asp Glu Asn Leu His Cys Val Pro  
                           85                          90                          95

Val Glu Thr Ala Asn Val Thr Met Gln Leu Leu Lys Ile Arg Ser Gly  
                           100                          105                          110

Asp Arg Pro Ser Tyr Val Glu Leu Thr Phe Ser Gln His Val Arg Cys  
                           115                          120                          125

Glu Cys Arg His Ser Pro Gly Arg Gln Ser Pro Asp Met Pro Gly Asp  
                           130                          135                          140

Phe Arg Ala Asp Ala Pro Ser Phe Leu Pro Pro Arg Arg Ser Leu Pro  
   145                          150                          155                          160

Met Leu Phe Arg Met Glu Trp Gly Cys Ala Leu Thr Gly Ser Gln Ser  
                           165                          170                          175

Ala Val Trp Pro Ser Ser Pro Val Pro Glu Glu Ile Pro Arg Met His  
                           180                          185                          190

Pro Gly Arg Asn Gly Lys Lys Gln Gln Arg Lys Pro Leu Arg Glu Lys  
                           195                          200                          205

Met Lys Pro Glu Arg Cys Gly Asp Ala Val Pro Arg Arg  
   210                          215                          220

&lt;210&gt; 129

&lt;211&gt; 1356

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&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 129

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Met Gln Ser Lys Val Leu Leu Ala Val Ala Leu Trp Leu Cys Val Glu
 1          5          10          15

Thr Arg Ala Ala Ser Val Gly Leu Pro Ser Val Ser Leu Asp Leu Pro
          20          25          30

Arg Leu Ser Ile Gln Lys Asp Ile Leu Thr Ile Lys Ala Asn Thr Thr
          35          40          45

Leu Gln Ile Thr Cys Arg Gly Gln Arg Asp Leu Asp Trp Leu Trp Pro
          50          55          60

Asn Asn Gln Ser Gly Ser Glu Gln Arg Val Glu Val Thr Glu Cys Ser
 65          70          75          80

Asp Gly Leu Phe Cys Lys Thr Leu Thr Ile Pro Lys Val Ile Gly Asn
          85          90          95

Asp Thr Gly Ala Tyr Lys Cys Phe Tyr Arg Glu Thr Asp Leu Ala Ser
          100          105          110

Val Ile Tyr Val Tyr Val Gln Asp Tyr Arg Ser Pro Phe Ile Ala Ser
          115          120          125

Val Ser Asp Gln His Gly Val Val Tyr Ile Thr Glu Asn Lys Asn Lys
          130          135          140

Thr Val Val Ile Pro Cys Leu Gly Ser Ile Ser Asn Leu Asn Val Ser
          145          150          155          160

Leu Cys Ala Arg Tyr Pro Glu Lys Arg Phe Val Pro Asp Gly Asn Arg
          165          170          175

Ile Ser Trp Asp Ser Lys Lys Gly Phe Thr Ile Pro Ser Tyr Met Ile
          180          185          190

Ser Tyr Ala Gly Met Val Phe Cys Glu Ala Lys Ile Asn Asp Glu Ser
          195          200          205

Tyr Gln Ser Ile Met Tyr Ile Val Val Val Val Gly Tyr Arg Ile Tyr
          210          215          220

Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
          225          230          235          240

Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
          245          250          255

Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
          260          265          270

Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
          275          280          285

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Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu  
 290 295 300  
 Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr  
 305 310 315 320  
 Phe Val Arg Val His Glu Lys Pro Phe Val Ala Phe Gly Ser Gly Met  
 325 330 335  
 Glu Ser Leu Val Glu Ala Thr Val Gly Glu Arg Val Arg Ile Pro Ala  
 340 345 350  
 Lys Tyr Leu Gly Tyr Pro Pro Pro Glu Ile Lys Trp Tyr Lys Asn Gly  
 355 360 365  
 Ile Pro Leu Glu Ser Asn His Thr Ile Lys Ala Gly His Val Leu Thr  
 370 375 380  
 Ile Met Glu Val Ser Glu Arg Asp Thr Gly Asn Tyr Thr Val Ile Leu  
 385 390 395 400  
 Thr Asn Pro Ile Ser Lys Glu Lys Gln Ser His Val Val Ser Leu Val  
 405 410 415  
 Val Tyr Val Pro Pro Gln Ile Gly Glu Lys Ser Leu Ile Ser Pro Val  
 420 425 430  
 Asp Ser Tyr Gln Tyr Gly Thr Thr Gln Thr Leu Thr Cys Thr Val Tyr  
 435 440 445  
 Ala Ile Pro Pro Pro His His Ile His Trp Tyr Trp Gln Leu Glu Glu  
 450 455 460  
 Glu Cys Ala Asn Glu Pro Ser Gln Ala Val Ser Val Thr Asn Pro Tyr  
 465 470 475 480  
 Pro Cys Glu Glu Trp Arg Ser Val Glu Asp Phe Gln Gly Gly Asn Lys  
 485 490 495  
 Ile Glu Val Asn Lys Asn Gln Phe Ala Leu Ile Glu Gly Lys Asn Lys  
 500 505 510  
 Thr Val Ser Thr Leu Val Ile Gln Ala Ala Asn Val Ser Ala Leu Tyr  
 515 520 525  
 Lys Cys Glu Ala Val Asn Lys Val Gly Arg Gly Glu Arg Val Ile Ser  
 530 535 540  
 Phe His Val Thr Arg Gly Pro Glu Ile Thr Leu Gln Pro Asp Met Gln  
 545 550 555 560  
 Pro Thr Glu Gln Glu Ser Val Ser Leu Trp Cys Thr Ala Asp Arg Ser  
 565 570 575  
 Thr Phe Glu Asn Leu Thr Trp Tyr Lys Leu Gly Pro Gln Pro Leu Pro  
 580 585 590



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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | His | Val | Gly | Glu | Leu | Pro | Thr | Pro | Val | Cys | Lys | Asn | Leu | Asp | Thr | 595 | 600 | 605 |
| Leu | Trp | Lys | Leu | Asn | Ala | Thr | Met | Phe | Ser | Asn | Ser | Thr | Asn | Asp | Ile | 610 | 615 | 620 |
| Leu | Ile | Met | Glu | Leu | Lys | Asn | Ala | Ser | Leu | Gln | Asp | Gln | Gly | Asp | Tyr | 625 | 630 | 635 |
| Val | Cys | Leu | Ala | Gln | Asp | Arg | Lys | Thr | Lys | Lys | Arg | His | Cys | Val | Val | 645 | 650 | 655 |
| Arg | Gln | Leu | Thr | Val | Leu | Glu | Arg | Val | Ala | Pro | Thr | Ile | Thr | Gly | Asn | 660 | 665 | 670 |
| Leu | Glu | Asn | Gln | Thr | Thr | Ser | Ile | Gly | Glu | Ser | Ile | Glu | Val | Ser | Cys | 675 | 680 | 685 |
| Thr | Ala | Ser | Gly | Asn | Pro | Pro | Pro | Gln | Ile | Met | Trp | Phe | Lys | Asp | Asn | 690 | 695 | 700 |
| Glu | Thr | Leu | Val | Glu | Asp | Ser | Gly | Ile | Val | Leu | Lys | Asp | Gly | Asn | Arg | 705 | 710 | 715 |
| Asn | Leu | Thr | Ile | Arg | Arg | Val | Arg | Lys | Glu | Asp | Glu | Gly | Leu | Tyr | Thr | 725 | 730 | 735 |
| Cys | Gln | Ala | Cys | Ser | Val | Leu | Gly | Cys | Ala | Lys | Val | Glu | Ala | Phe | Phe | 740 | 745 | 750 |
| Ile | Ile | Glu | Gly | Ala | Gln | Glu | Lys | Thr | Asn | Leu | Glu | Ile | Ile | Ile | Leu | 755 | 760 | 765 |
| Val | Gly | Thr | Ala | Val | Ile | Ala | Met | Phe | Phe | Trp | Leu | Leu | Leu | Val | Ile | 770 | 775 | 780 |
| Ile | Leu | Arg | Thr | Val | Lys | Arg | Ala | Asn | Gly | Gly | Glu | Leu | Lys | Thr | Gly | 785 | 790 | 795 |
| Tyr | Leu | Ser | Ile | Val | Met | Asp | Pro | Asp | Glu | Leu | Pro | Leu | Asp | Glu | His | 805 | 810 | 815 |
| Cys | Glu | Arg | Leu | Pro | Tyr | Asp | Ala | Ser | Lys | Trp | Glu | Phe | Pro | Arg | Asp | 820 | 825 | 830 |
| Arg | Leu | Lys | Leu | Gly | Lys | Pro | Leu | Gly | Arg | Gly | Ala | Phe | Gly | Gln | Val | 835 | 840 | 845 |
| Ile | Glu | Ala | Asp | Ala | Phe | Gly | Ile | Asp | Lys | Thr | Ala | Thr | Cys | Arg | Thr | 850 | 855 | 860 |
| Val | Ala | Val | Lys | Met | Leu | Lys | Glu | Gly | Ala | Thr | His | Ser | Glu | His | Arg | 865 | 870 | 875 |
| Ala | Leu | Met | Ser | Glu | Leu | Lys | Ile | Leu | Ile | His | Ile | Gly | His | His | Leu | 885 | 890 | 895 |

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|      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |     |
|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|-----|
| Asn  | Val  | Val  | Asn  | Leu  | Leu  | Gly  | Ala  | Cys  | Thr  | Lys  | Pro  | Gly  | Gly  | Pro  | Leu |
|      |      |      | 900  |      |      |      |      | 905  |      |      |      |      | 910  |      |     |
| Met  | Val  | Ile  | Val  | Glu  | Phe  | Cys  | Lys  | Phe  | Gly  | Asn  | Leu  | Ser  | Thr  | Tyr  | Leu |
|      |      | 915  |      |      |      |      | 920  |      |      |      |      | 925  |      |      |     |
| Arg  | Ser  | Lys  | Arg  | Asn  | Glu  | Phe  | Val  | Pro  | Tyr  | Lys  | Thr  | Lys  | Gly  | Ala  | Arg |
|      | 930  |      |      |      |      | 935  |      |      |      |      | 940  |      |      |      |     |
| Phe  | Arg  | Gln  | Gly  | Lys  | Asp  | Tyr  | Val  | Gly  | Ala  | Ile  | Pro  | Val  | Asp  | Leu  | Lys |
| 945  |      |      |      |      | 950  |      |      |      |      | 955  |      |      |      |      | 960 |
| Arg  | Arg  | Leu  | Asp  | Ser  | Ile  | Thr  | Ser  | Ser  | Gln  | Ser  | Ser  | Ala  | Ser  | Ser  | Gly |
|      |      |      |      | 965  |      |      |      |      | 970  |      |      |      |      | 975  |     |
| Phe  | Val  | Glu  | Glu  | Lys  | Ser  | Leu  | Ser  | Asp  | Val  | Glu  | Glu  | Glu  | Glu  | Ala  | Pro |
|      |      |      | 980  |      |      |      |      | 985  |      |      |      |      | 990  |      |     |
| Glu  | Asp  | Leu  | Tyr  | Lys  | Asp  | Phe  | Leu  | Thr  | Leu  | Glu  | His  | Leu  | Ile  | Cys  | Tyr |
|      |      | 995  |      |      |      |      | 1000 |      |      |      |      | 1005 |      |      |     |
| Ser  | Phe  | Gln  | Val  | Ala  | Lys  | Gly  | Met  | Glu  | Phe  | Leu  | Ala  | Ser  | Arg  | Lys  | Cys |
|      | 1010 |      |      |      |      | 1015 |      |      |      |      | 1020 |      |      |      |     |
| Ile  | His  | Arg  | Asp  | Leu  | Ala  | Ala  | Arg  | Asn  | Ile  | Leu  | Leu  | Ser  | Glu  | Lys  | Asn |
| 1025 |      |      |      | 1030 |      |      |      |      | 1035 |      |      |      |      | 1040 |     |
| Val  | Val  | Lys  | Ile  | Cys  | Asp  | Phe  | Gly  | Leu  | Ala  | Arg  | Asp  | Ile  | Tyr  | Lys  | Asp |
|      |      |      | 1045 |      |      |      |      | 1050 |      |      |      |      | 1055 |      |     |
| Pro  | Asp  | Tyr  | Val  | Arg  | Lys  | Gly  | Asp  | Ala  | Arg  | Leu  | Pro  | Leu  | Lys  | Trp  | Met |
|      |      | 1060 |      |      |      |      | 1065 |      |      |      |      | 1070 |      |      |     |
| Ala  | Pro  | Glu  | Thr  | Ile  | Phe  | Asp  | Arg  | Val  | Tyr  | Thr  | Ile  | Gln  | Ser  | Asp  | Val |
|      | 1075 |      |      |      |      | 1080 |      |      |      |      | 1085 |      |      |      |     |
| Trp  | Ser  | Phe  | Gly  | Val  | Leu  | Leu  | Trp  | Glu  | Ile  | Phe  | Ser  | Leu  | Gly  | Ala  | Ser |
|      | 1090 |      |      |      | 1095 |      |      |      |      | 1100 |      |      |      |      |     |
| Pro  | Tyr  | Pro  | Gly  | Val  | Lys  | Ile  | Asp  | Glu  | Glu  | Phe  | Cys  | Arg  | Arg  | Leu  | Lys |
| 1105 |      |      |      | 1110 |      |      |      |      | 1115 |      |      |      |      | 1120 |     |
| Glu  | Gly  | Thr  | Arg  | Met  | Arg  | Ala  | Pro  | Asp  | Tyr  | Thr  | Thr  | Pro  | Glu  | Met  | Tyr |
|      |      |      | 1125 |      |      |      |      | 1130 |      |      |      | 1135 |      |      |     |
| Gln  | Thr  | Met  | Leu  | Asp  | Cys  | Trp  | His  | Gly  | Glu  | Pro  | Ser  | Gln  | Arg  | Pro  | Thr |
|      |      | 1140 |      |      |      |      | 1145 |      |      |      |      | 1150 |      |      |     |
| Phe  | Ser  | Glu  | Leu  | Val  | Glu  | His  | Leu  | Gly  | Asn  | Leu  | Leu  | Gln  | Ala  | Asn  | Ala |
|      | 1155 |      |      |      |      | 1160 |      |      |      |      | 1165 |      |      |      |     |
| Gln  | Gln  | Asp  | Gly  | Lys  | Asp  | Tyr  | Ile  | Val  | Leu  | Pro  | Ile  | Ser  | Glu  | Thr  | Leu |
| 1170 |      |      |      |      | 1175 |      |      |      |      | 1180 |      |      |      |      |     |
| Ser  | Met  | Glu  | Glu  | Asp  | Ser  | Gly  | Leu  | Ser  | Leu  | Pro  | Thr  | Ser  | Pro  | Val  | Ser |
| 1185 |      |      |      | 1190 |      |      |      |      | 1195 |      |      |      |      | 1200 |     |

|     |     |     |     |      |     |     |     |     |      |     |     |     |     |      |     |  |
|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|--|
| Cys | Met | Glu | Glu | Glu  | Glu | Val | Cys | Asp | Pro  | Lys | Phe | His | Tyr | Asp  | Asn |  |
|     |     |     |     | 1205 |     |     |     |     | 1210 |     |     |     |     | 1215 |     |  |
| Thr | Ala | Gly | Ile | Ser  | Gln | Tyr | Leu | Gln | Asn  | Ser | Lys | Arg | Lys | Ser  | Arg |  |
|     |     |     |     | 1220 |     |     |     |     | 1225 |     |     |     |     | 1230 |     |  |
| Pro | Val | Ser | Val | Lys  | Thr | Phe | Glu | Asp | Ile  | Pro | Leu | Glu | Glu | Pro  | Glu |  |
|     |     |     |     | 1235 |     |     |     |     | 1240 |     |     |     |     | 1245 |     |  |
| Val | Lys | Val | Ile | Pro  | Asp | Asp | Asn | Gln | Thr  | Asp | Ser | Gly | Met | Val  | Leu |  |
|     |     |     |     | 1250 |     |     |     |     | 1255 |     |     |     |     | 1260 |     |  |
| Ala | Ser | Glu | Glu | Leu  | Lys | Thr | Leu | Glu | Asp  | Arg | Thr | Lys | Leu | Ser  | Pro |  |
|     |     |     |     | 1265 |     |     |     |     | 1270 |     |     |     |     | 1275 |     |  |
| Ser | Phe | Gly | Gly | Met  | Val | Pro | Ser | Lys | Ser  | Arg | Glu | Ser | Val | Ala  | Ser |  |
|     |     |     |     | 1285 |     |     |     |     | 1290 |     |     |     |     | 1295 |     |  |
| Glu | Gly | Ser | Asn | Gln  | Thr | Ser | Gly | Tyr | Gln  | Ser | Gly | Tyr | His | Ser  | Asp |  |
|     |     |     |     | 1300 |     |     |     |     | 1305 |     |     |     |     | 1310 |     |  |
| Asp | Thr | Asp | Thr | Thr  | Val | Tyr | Ser | Ser | Glu  | Glu | Ala | Glu | Leu | Leu  | Lys |  |
|     |     |     |     | 1315 |     |     |     |     | 1320 |     |     |     |     | 1325 |     |  |
| Leu | Ile | Glu | Ile | Gly  | Val | Gln | Thr | Gly | Ser  | Thr | Ala | Gln | Ile | Leu  | Gln |  |
|     |     |     |     | 1330 |     |     |     |     | 1335 |     |     |     |     | 1340 |     |  |
| Pro | Asp | Ser | Gly | Thr  | Thr | Leu | Ser | Ser | Pro  | Pro | Val |     |     |      |     |  |
|     |     |     |     | 1345 |     |     |     |     | 1350 |     |     |     |     | 1355 |     |  |

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<210> 130
<211> 98
<212> PRT
<213> Homo sapiens
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|           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| <400> 130 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Met       | Asn | Gln | Thr | Ala | Ile | Leu | Ile | Cys | Cys | Leu | Ile | Phe | Leu | Thr | Leu |
| 1         |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Ser       | Gly | Ile | Gln | Gly | Val | Pro | Leu | Ser | Arg | Thr | Val | Arg | Cys | Thr | Cys |
|           |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Ile       | Ser | Ile | Ser | Asn | Gln | Pro | Val | Asn | Pro | Arg | Ser | Leu | Glu | Lys | Leu |
|           |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Glu       | Ile | Ile | Pro | Ala | Ser | Gln | Phe | Cys | Pro | Arg | Val | Glu | Ile | Ile | Ala |
|           | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Thr       | Met | Lys | Lys | Lys | Gly | Glu | Lys | Arg | Cys | Leu | Asn | Pro | Glu | Ser | Lys |
| 65        |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| Ala       | Ile | Lys | Asn | Leu | Leu | Lys | Ala | Val | Ser | Lys | Glu | Met | Ser | Lys | Arg |
|           |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

Ser Pro

107/147

<210> 131  
 <211> 94  
 <212> PRT  
 <213> Homo sapiens

<400> 131  
 Met Ser Val Lys Gly Met Ala Ile Ala Leu Ala Val Ile Leu Cys Ala  
     1                    5                    10                    15  
 Thr Val Val Gln Gly Phe Pro Met Phe Lys Arg Gly Arg Cys Leu Cys  
             20                    25                    30  
 Ile Gly Pro Gly Val Lys Ala Val Lys Val Ala Asp Ile Glu Lys Ala  
             35                    40                    45  
 Ser Ile Met Tyr Pro Ser Asn Asn Cys Asp Lys Ile Glu Val Ile Ile  
       50                    55                    60  
 Thr Leu Lys Glu Asn Lys Gly Gln Arg Cys Leu Asn Pro Lys Ser Lys  
   65                    70                    75                    80  
 Gln Ala Arg Leu Ile Ile Lys Lys Val Glu Arg Lys Asn Phe  
             85                    90

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 <211> 5102  
 <212> DNA  
 <213> Homo sapiens

<400> 132  
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 tgataatgca cgaggagggc gaggtggacg gcaaagccat tcctgacctc accgcgccccg 180  
 tggccgcgct gcaggcggcc gtcagcaacc tcgtccgggt tggaaaagag actgttcaaa 240  
 ccactgagga tcagattttg aagagagata tgccaccagc atttattaag gttgagaatg 300  
 cttgcaccaa gcttgtccag gcagctcaga tgcttcagtc agacccttac tcagtgcctg 360  
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108/147

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| gggagagtcc | tcaggcacga  | gcacttgcac  | ctcagctcca | agactcctta | aaggatctaa  | 1800 |
| aagctcggat | gcaggaggcc  | atgactcagg  | aagtgtcaga | tgttttcagc | gataaccaca  | 1860 |
| ctcccatcaa | gctgttggca  | gtggcagcca  | cggcgcctcc | tgatgcgcct | aacagggaag  | 1920 |
| aggtatttga | tgagagggca  | gctaactttg  | aaaaccattc | aggaaagctt | ggtgctacgg  | 1980 |
| ccgagaaggc | ggctgcggtt  | ggtactgcta  | ataaatcaac | agtggaaggc | attcaggcct  | 2040 |
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| aagctgcctc | tgatgaattg  | agcaaaacca  | tctccccaat | ggtgatggat | gcaaaagctg  | 2460 |
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| cgctccacc  | agacettgaa  | caactccgac  | taacagatga | gcttgctcct | cccaaaccac  | 2640 |
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| aaatgatctg | agtcccagga  | gctgcccaga  | tgtgtggga  | gctgaaaaat | cacatcctgg  | 3360 |
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&lt;213&gt; Homo sapiens

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&lt;210&gt; 134

&lt;211&gt; 3622

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 134

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|             |             |            |             |             |             |      |
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| gcgcgagtcg  | acaagtaaga  | gtgcgggagg | catcttaatt  | aaccctgctg  | tccctggagc  | 1080 |
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| cggccccgaa  | acttgctgctg | gcacgcaaaa | ctaacctcac  | gtgaagttag  | ggactgttct  | 1260 |
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| ctcacctcgc  | ccgacgtggg  | gctgctcaag | ctggcgctgc  | ccgagctgga  | gcgcctgata  | 1500 |
| atccagtcca  | gcaacgggca  | catcaccacc | acgcgcgacc  | ccaccagctt  | cctgtgcccc  | 1560 |
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| aggaaccgca  | tcgctgcctc  | caagtgcgca | aaaagggaagc | tggagagaat  | cgcccggctg  | 2100 |
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| tgtctctgta  | gtactcctta  | agaacacaaa | gcggggggag  | ggttggggag  | ggcggcgagg  | 2700 |
| aggaggggtt  | gtgagagcga  | ggctgagcct | acagatgaac  | tctttctggc  | ctgctttcgt  | 2760 |
| taactgtgta  | tgtacatata  | tatatTTTTT | aatttgatta  | aagctgatta  | ctgtcaataa  | 2820 |
| acagcttcat  | gcctttgtaa  | gttattttct | gtttgtttgt  | ttgggtatcc  | tgcccagtg   | 2880 |
| tgtttgtaaa  | taagagattt  | ggagcactct | gagtttaacca | tttgtaataa  | agtatataat  | 2940 |
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| ttggaaagta  | ctccccctaac | ctcttttctg | catcatctgt  | agatcctagt  | ctatctaggt  | 3060 |
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| gaagtcaaac  | atttcaaaagt | ttggattgca | tcaagtggca  | tgtgctgtga  | ccattttataa | 3360 |
| tgttagaaat  | tttacaatag  | gtgcttattc | tcaaagcagg  | aattgggtggc | agattttaca  | 3420 |
| aaagatgtat  | ccttccaatt  | tggaatcttc | tctttgacaa  | ttcctagata  | aaaagatggc  | 3480 |
| ctttgtctta  | tgaatatatta | taacagcatt | ctgtcacaa   | aaatgtattc  | aaataccaat  | 3540 |
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&lt;210&gt; 135

&lt;211&gt; 6210

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 135

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| cttccacgct | ttgcactgaa | ttagggctag | aattggggat | gggggtaggg | gcgcattcct | 120 |
| tcgggagccg | aggcttaagt | cctcggggct | ctgtactcga | tgccgtttct | cctatctctg | 180 |
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|             |             |             |             |             |             |      |
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| catattagga  | catctgcgtc  | agcaggtttc  | cacggccttt  | ccctgtagcc  | ctggggggag  | 480  |
| ccatccccga  | aacccctcat  | cttggggggc  | ccacgagacc  | tctgagacag  | gaactgcgaa  | 540  |
| atgctcacga  | gattaggaca  | cgcgccaagg  | cgggggcagg  | gagctgcgag  | cgctggggac  | 600  |
| gcagccgggc  | ggccgcagaa  | gcgcccaggc  | ccgcgcgcca  | cccctctggc  | gccaccgtgg  | 660  |
| ttgagcccg   | gacgtttaca  | ctcattcata  | aaacgcttgt  | tataaaagca  | gtggctgcgg  | 720  |
| cgctcgtac   | tccaaccgca  | tctgcagcga  | gcaactgaga  | agccaagact  | gagccggcgg  | 780  |
| ccgcgggcga  | gcgaacgagc  | agtgaaccgtg | ctcctaccca  | gctctgcttc  | acagcgccca  | 840  |
| cctgtctccg  | cccctcgggc  | cctcgcccg   | ctttgcctaa  | ccgccacgat  | gatgtttctg  | 900  |
| ggcttcaacg  | cagactacga  | ggcgtcatcc  | tcccgtgca   | gcagcgcgtc  | cccggccggg  | 960  |
| gatagccctc  | cttactacca  | ctcaccgcga  | gactccttct  | ccagcatggg  | ctcgccctgtc | 1020 |
| aacgcgcagg  | taaggctggc  | ttcccgctgc  | cgcggggccc  | ggggcttggg  | gtcgcgagg   | 1080 |
| aggagacacc  | gggcgggacg  | ctccagtaga  | tgagtagggg  | gctcccttgt  | gcctggagg   | 1140 |
| aggctgccgt  | ggccggagcg  | gtgccggctc  | gggggctcgg  | gacttgctct  | gagcgcacgc  | 1200 |
| acgcttgcca  | tagtaagaat  | tggttcccc   | ttcgggaggc  | aggttcgttc  | tgagcaacct  | 1260 |
| ctggtctgca  | ctccaggacg  | gatctctgac  | attagctgga  | gcagacgtgt  | cccaagcaca  | 1320 |
| aactcgctaa  | ctagagccctg | gcttcttcgg  | ggagggtggca | gaaagcggca  | atccccctc   | 1380 |
| ccccggcagc  | ctggagcacg  | gaggagggat  | gagggaggag  | ggtgcagcgg  | gcgggtgtgt  | 1440 |
| aaggcagttt  | cattgataaa  | aagcgagttc  | attctggaga  | ctccggagcg  | gcgcctgcgt  | 1500 |
| cagcgcagac  | gtcagggata  | tttataacaa  | accccctttc  | aagcaagtga  | tgctgaagg   | 1560 |
| ataacgggaa  | cgcagcggca  | ggatggaaga  | gacaggcact  | gcgctgcgga  | atgcctggga  | 1620 |
| ggaaaagggg  | gagacctttc  | atccaggatg  | agggacattt  | aagatgaaat  | gtccgtggca  | 1680 |
| ggatcgtttc  | tcttcaactgc | tgcatgcggc  | actgggaact  | cgccccacct  | gtgtccggaa  | 1740 |
| cctgctcgct  | cacgtcggct  | ttccccttct  | gttttgttct  | aggacttctg  | cacggacctg  | 1800 |
| gccgtctcca  | gtgccaactt  | cattcccacg  | gtcactgcca  | tctcgaccag  | tccggacctg  | 1860 |
| cagtggctgg  | tgcagcccg   | cctcgtctcc  | tctgtggccc  | catcgacagc  | cagagccct   | 1920 |
| caccctttcg  | gagtccccg   | cccctccgct  | ggggcttact  | ccagggtctg  | cgttgtgaag  | 1980 |
| accatgacag  | gaggccgagc  | gcagagcatt  | ggcaggagg   | gcaagggtga  | acaggtagag  | 2040 |
| aactctagcg  | tactcttcc   | gggaatgtgg  | gggctgggtg  | ggaagcagcc  | ccggagatgc  | 2100 |
| aggagcccag  | tacagaggat  | gaagccactg  | atggggctgg  | ctgcacatcc  | gtaactggga  | 2160 |
| gccctggctc  | caagcccat   | ccatcccac   | tcagactctg  | agtctcacc   | taagaagtac  | 2220 |
| tctcatagtt  | tcttccctaa  | gtttcttacc  | gcactgtttc  | agactgggt   | cttctttgtt  | 2280 |
| ctcttgctga  | ggatcttatt  | ttaaatgcaa  | gtcacacct   | ttctgcaact  | gcaggtcaga  | 2340 |
| aatggtttca  | cagtgggtg   | ccaggaagca  | gggaagctgc  | aggagccagt  | tctactgggg  | 2400 |
| tgggtgaatg  | gaggtgatgg  | cagacacttt  | tactgaatgt  | cggctctttt  | ttgtgattat  | 2460 |
| tctagttatc  | tccagaagaa  | gaagagaaaa  | ggagaatccg  | aagggaaagg  | aataagatgg  | 2520 |
| ctgcagccaa  | atgccgcaac  | cggaggagg   | agctgactga  | tacactccaa  | gcggtaggta  | 2580 |
| ctctgtgggt  | tgctcctttt  | taaaacttaa  | gggaaagtgt  | gagattgagc  | ataagggcc   | 2640 |
| ttgagtaaga  | ctgtgtctta  | tgctttcctt  | tatccctctg  | tatacaggag  | acagaccaac  | 2700 |
| tagaagatga  | gaagtctgct  | ttgcagaccg  | agattgccaa  | cctgctgaag  | gagaaggaaa  | 2760 |
| aactagagtt  | catcctggca  | gctcaccgac  | ctgcctgcaa  | gatccctgat  | gacctgggct  | 2820 |
| tcccagaaga  | gatgtctgtg  | gcttcccttg  | atctgactgg  | gggcttgcca  | gaggttgcca  | 2880 |
| ccccggagtc  | tgaggaggcc  | ttcaccctgc  | ctctcctcaa  | tgaccctgag  | cccaagccct  | 2940 |
| cagtggaacc  | tgtcaagagc  | atcagcagca  | tggagctgaa  | gaccgagccc  | tttgatgact  | 3000 |
| tctgtttccc  | agcatcatcc  | aggcccagtg  | gctctgagac  | agcccgtctc  | gtgccagaca  | 3060 |
| tggacctatc  | tgggtccttc  | tatgcagcag  | actgggagcc  | tctgcacagt  | ggctccctgg  | 3120 |
| ggatggggcc  | catggccaca  | gagctggagc  | ccctgtggac  | tccggtggte  | acctgtactc  | 3180 |
| ccagctgcac  | tgcttacacg  | tcttccctcg  | tcttcacct   | ccccgaggct  | gactccttcc  | 3240 |
| ccagctgtgc  | agctgccac   | cgcaagggca  | gcagcagcaa  | tgagccttcc  | tctgactcgc  | 3300 |
| tcagctcacc  | cacgtgctg   | gccctgtgag  | ggggcaggga  | aggggaggca  | gccggcacc   | 3360 |
| acaagtgcca  | ctgcccagc   | tgggtgatta  | cagagaggag  | aaacacatct  | tccctagagg  | 3420 |
| gttccctgtag | acctaggagg  | gaccttatct  | gtgcgtgaaa  | cacaccaggc  | tgtgggcctc  | 3480 |
| aaggacttga  | aagcatccat  | gtgtggactc  | aagtccttac  | ctcttccgga  | gatgtagcaa  | 3540 |
| aacgcattgga | gtgtgtattg  | ttcccagtga  | cacttcagag  | agctggtagt  | tagtagcatg  | 3600 |
| ttgagccagg  | cctgggtctg  | tgtctctttt  | ctctttctcc  | ttagtcttct  | catagcatta  | 3660 |
| actaatctat  | tgggttcatt  | attggaatta  | acctggtgct  | ggatattttc  | aaattgtatc  | 3720 |



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|             |             |             |             |            |             |      |
|-------------|-------------|-------------|-------------|------------|-------------|------|
| tagtgcagct  | gattttaaaca | ataactactg  | tgttctctggc | aatagtgtgt | tctgattaga  | 3780 |
| aatgaccaat  | attatactaa  | gaaaagatac  | gactttatatt | tctggtagat | agaaataaat  | 3840 |
| agctatatcc  | atgtactgta  | gtttttcttc  | aacatcaatg  | ttcattgtaa | tgttactgat  | 3900 |
| catgcattgt  | tgagggtggtc | tgaatgttct  | gacattaaca  | gttttccatg | aaaacgtttt  | 3960 |
| atttgtgttt  | taatttatatt | attaagatgg  | attctcagat  | atttatattt | ttattttatt  | 4020 |
| tttttctacc  | ttgaggtctt  | ttgacatgtg  | gaaagtgaat  | ttgaatgaaa | aattttaagca | 4080 |
| ttgtttgctt  | attgttccaa  | gacattgtca  | ataaaagcat  | ttaagttgaa | tgcgaccaac  | 4140 |
| cttgtgctct  | tttcattctg  | gaagtcttgt  | aagtttctga  | aaggtattat | tgagagaccag | 4200 |
| tttgtcaaga  | agggtagctg  | ctggaggggg  | acacaccctc  | tgtctgatcc | cttatcaaaag | 4260 |
| aggacaagga  | aactatagag  | ctgatttttag | aataattttac | aaatacatgc | cttccatttg  | 4320 |
| aatgctaaga  | ttttctactg  | cttctgggga  | cgggaaaccg  | ctgtgtaaca | gcttttgttg  | 4380 |
| gaatacatatt | tttctgtttc  | agtactcgca  | gggggaaata  | tttaaatttt | gttgtgctaa  | 4440 |
| tattaaattc  | agatgttttg  | atcttaaagg  | aaccttttaa  | gcaaacagaa | cctagctttg  | 4500 |
| tacagactat  | tttaactttt  | tattctcaca  | aaatcacgtg  | gagggttatt | ctacttcaaa  | 4560 |
| gatgagcaaa  | ttgaagaatg  | gttagaataa  | acaactttct  | tgatattccg | ttatcggcat  | 4620 |
| tagaatcttc  | ctgctcggtt  | tcgtatccag  | caggctgaac  | tgctcttgta | tacttggtta  | 4680 |
| aaaaaaattt  | tcaggccggg  | cgcggtggcc  | catgcctgta  | atcctagcac | tttgggaggc  | 4740 |
| cgaggcaggc  | ggatcacctg  | aggtcgggag  | ttcgagacca  | gcctgaccaa | catggagaaa  | 4800 |
| ccccgtcttt  | actaaaaata  | caaaattagc  | ctggtgtggt  | ggtgcatgcc | tgtaatccta  | 4860 |
| gctacttgag  | aggctgagac  | aggaaaatca  | cttgaactcg  | ggaggcggat | gttgacgcga  | 4920 |
| actgagattg  | cgccattgca  | ctccagcctg  | ggcaacaaga  | ttgaaactct | gtttaaaaaa  | 4980 |
| aaaagttttc  | actaatgtgt  | acattttttt  | gtactctttt  | attctcgaaa | gggaaggagg  | 5040 |
| gctattgccc  | tatcccttat  | taataaatgc  | atttgtggtt  | ctggtttctc | taataccata  | 5100 |
| tgcccttcat  | tcagtttata  | gtgggcgga   | gtgggggaga  | aaaagttgct | cagaaatcaa  | 5160 |
| aagatatctc  | aaacagcaca  | aataatggct  | gatcgttctg  | caaacaaaaa | gttacataat  | 5220 |
| agctcaagaa  | ggagaagtca  | acatgactct  | gaacaagctt  | taacttagaa | actttatcat  | 5280 |
| cttaaggaag  | aacgtgacct  | ttgtccagga  | cgtctctggt  | aatggggcac | ttacacacac  | 5340 |
| atgcacacgt  | acaaaccaca  | gggaaaggag  | accgcccttc  | tgctctgct  | cgcgagtatc  | 5400 |
| acgcaggcac  | catgcactat  | gttttcacac  | acactgggtg  | gaagaagagc | ttcagcgcca  | 5460 |
| gtcttcta    | gctttggtga  | taatgaaat   | cactgggtgc  | ttatggggtg | tcataattcaa | 5520 |
| tcgagttaaa  | agtttttaatt | caaaatgaca  | gttttactga  | ggttgatgtt | ctcgtctatg  | 5580 |
| atatctctgc  | ccctcccata  | aaaatggaca  | ttttaaagca  | acttaccgct | ctttagatca  | 5640 |
| ctcctatata  | acacaccact  | tggggtgctg  | tttctgctag  | acttgtgatg | acagtggcct  | 5700 |
| taggatccct  | gtttgctgtt  | caaagggcaa  | atattttata  | gcctttaaat | atacctaaac  | 5760 |
| taaatacaga  | attaatataa  | ctaacaaaca  | cctgggtctga | aataacaagg | tgatctaccc  | 5820 |
| tgggaaggaac | ccagctggtg  | ggccaggagc  | ggtggctcac  | acctgtaatt | ccagcacttt  | 5880 |
| gggaggctga  | gacaggagga  | tcactggagt  | ccaggagttt  | gagaccagcc | tgggcaacat  | 5940 |
| ggcaaaacc   | agtgtgcttc  | tgttgtccca  | gtagaactac  | tcaggaggct | gaggcaggag  | 6000 |
| tatgacttga  | gcctaggagg  | gggaggttgc  | agagaactga  | tattgcacca | ccactgcact  | 6060 |
| ccagcctggg  | tgacacagca  | aaaccctatc  | tcaaaaaaaa  | aaaaaaaaaa | aaggaaacca  | 6120 |
| gctggttctc  | gtaggtgtgc  | aataataaca  | accagaggaa  | gaaaaggaag | acgatttccc  | 6180 |
| agatgaagaa  | gggcagctgg  | accttcggac  |             |            |             | 6210 |

&lt;210&gt; 136

&lt;211&gt; 1714

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 136

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| gctcgggccc | cgagtctgct | cgctgacgtc | cgacgtccca | ggtactttcc | ccacggccga | 60  |
| cagggtcttg | cgtggggg   | gggcgcggcg | cgcagcgcgc | atgcgccgca | gcgccagcgc | 120 |
| tctccccgga | tcgtgcgggg | cctgagcctc | tcogccggcg | caggctctgc | tcgcgccagc | 180 |
| tcgctccccg | agccatgccc | accaccatcg | agcgggagtt | cgaagagttg | gatactcagc | 240 |
| gtcgtgggca | gccgctgtac | ttggaaattc | gaaatgagtc | ccatgactat | cctcatagag | 300 |
| tggccaagtt | tccagaaaac | agaaatcgaa | acagatacag | agatgtaagc | ccatatgata | 360 |
| acagtcgtgt | taaactgcaa | aatgctgaga | atgattatat | taatgccagt | ttagttgaca | 420 |
| tagaagaggc | acaaaggagt | tacatcttaa | cacagggtcc | acttcctaac | acatgctgcc | 480 |

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|             |            |            |            |            |             |      |
|-------------|------------|------------|------------|------------|-------------|------|
| atttctggct  | tatggtttgg | cagcagaaga | ccaaagcagt | tgtcatgctg | aaccgcattg  | 540  |
| tggagaaaga  | atcggttaaa | tgtgcacagt | actggccaac | agatgacca  | gagatgctgt  | 600  |
| ttaaagaaac  | aggattcagt | gtgaagctct | tgtcagaaga | tgtgaagtcg | tattatacag  | 660  |
| tacatctact  | acaattagaa | aatatcaata | gtggtgaaac | cagaacaata | tctcactttc  | 720  |
| attatactac  | ctggccagat | tttggagtcc | ctgaatcacc | agcttcattt | ctcaattttct | 780  |
| tgtttaaagt  | gagagaatct | ggctccttga | accctgacca | tgggcctgcg | gtgatccact  | 840  |
| gtagtgcagg  | cattgggccc | tctggcacct | tctctctggt | agacacttgt | cttgttttga  | 900  |
| tggaaaaagg  | agatgatatt | aacataaaac | aagtgttact | gaacatgaga | aaataccgaa  | 960  |
| tgggtcttat  | tcagacccca | gatcaactga | gattctcata | catggctata | atagaaggag  | 1020 |
| caaaatgtat  | aaaggagat  | tctagtatac | agaaacgatg | gaaagaactt | tctaagggaag | 1080 |
| acttatctcc  | tgcttttgat | cattcaccaa | acaaaataat | gactgaaaaa | tacaatggga  | 1140 |
| acagaatagg  | tctagaagaa | gaaaaactga | caggtgaccg | atgtacagga | ctttcctcta  | 1200 |
| aaatgcaaga  | tacaatggag | gagaacagtg | agagtgtctt | acggaaacgt | attcgagagg  | 1260 |
| acagaaaggc  | caccacagct | cagaagggtg | agcagatgaa | acagaggcta | aatgagaatg  | 1320 |
| aacgaaaaag  | aaaaaggcca | agattgacag | acacctaata | ttcatgactt | gagaatatct  | 1380 |
| tgcagctata  | aattttgaac | cattgatgtg | caaagcaaga | cctgaagccc | actccggaaa  | 1440 |
| ctaaagtgag  | gctcgctaac | cctctagatt | gcctcacagt | tgtttgttta | caaagtaaac  | 1500 |
| tttacatcca  | gggatgaag  | agcaccacc  | agcagaagac | tttgcagaac | ctttaatttg  | 1560 |
| atgtgttaag  | tgtttttaat | gagtgtatga | aatgtagaaa | gatgtacaag | aaataaatta  | 1620 |
| ggagagatta  | ctttgtattg | tactgccatt | cctactgtat | ttttatactt | tttggcagca  | 1680 |
| ttaaataattt | ttgttaata  | aaaaaaaaaa | aaaa       |            |             | 1714 |

&lt;210&gt; 137

&lt;211&gt; 2213

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 137

|             |             |             |             |            |             |      |
|-------------|-------------|-------------|-------------|------------|-------------|------|
| ggaggcggca  | acattgtttc  | aagttggcca  | aattgacaag  | agcgagaggt | atactgcgtt  | 60   |
| ccatcccgac  | ccgggccacg  | gtactgggcc  | ctgtttcccc  | ctcctcggcc | cccagagacc  | 120  |
| agggtccgcc  | ttctgcaggg  | ttcccaggcc  | cccgcctccag | ggccgggctg | accgactcgc  | 180  |
| ctggcgcttc  | atggagaact  | tccaaaagggt | ggaaaagatc  | ggagagggca | cgtaaggagt  | 240  |
| tgtgtacaaa  | gccagaaaca  | agttgacggg  | agagggtggtg | gcgcttaaga | aaatccgcct  | 300  |
| ggacactgag  | actgagggtg  | tgcccagtag  | tgccatccga  | gagatctctc | tgcttaaggga | 360  |
| gcttaaccat  | cctaattattg | tcaagctgct  | ggatgtcatt  | cacacagaaa | ataaactcta  | 420  |
| cctggttttt  | gaattttctgc | accaagatct  | caagaaattc  | atggatgcct | ctgctctcac  | 480  |
| tggcattcct  | cttccctca   | tcaagagcta  | tctgttccag  | ctgctccagg | gcctagcttt  | 540  |
| ctgcattctt  | catcgggtcc  | tccaccgaga  | ccttaaacct  | cagaatctgc | ttattaacac  | 600  |
| agagggggcc  | atcaagctag  | cagactttgg  | actagccaga  | gcttttggag | tccctgttcg  | 660  |
| tacttacacc  | catgagggtg  | tgaccctgtg  | gtaccgagct  | cctgaaatcc | tccctgggctg | 720  |
| caaataattat | tccacagctg  | tggacatctg  | gagcctgggc  | tgcactcttg | ctgagatggt  | 780  |
| gactcgccgg  | gccctattcc  | ctggagattc  | tgagattgac  | cagctcttcc | ggatctttcg  | 840  |
| gactctgggg  | acccagatg   | aggtggtgtg  | gccaggagtt  | acttctatgc | ctgattacaa  | 900  |
| gccaagtttc  | cccaagtggg  | cccggcaaga  | ttttagtaaa  | gttgtagctc | ccctggatga  | 960  |
| agatggacgg  | agcttggtat  | cgcaaagtgt  | gcactacgac  | cctaacaagc | ggatttcggc  | 1020 |
| caaggcagcc  | ctggctcacc  | ctttcttcca  | ggatgtgacc  | aagccagtac | cccattcttcg | 1080 |
| actctgatag  | ccttcttgaa  | gccccagcc   | ctaactctac  | cctctctctc | agtgtgggct  | 1140 |
| tgaccaggct  | tgcgcttggg  | ctatttggac  | tcaggtgggc  | cctctgaact | tgctttaaacc | 1200 |
| actcaccttc  | tagtcttggc  | cagccaaactc | tgggaatata  | ggggtgaaag | gggggaacca  | 1260 |
| gtgaaaatga  | aaggaagttt  | cagtattaga  | tgcacttaag  | ttagcctcca | ccaccctttc  | 1320 |
| ccccttctct  | tagttattgc  | tgaagagggt  | tggatataaaa | ataattttta | aaaagccttc  | 1380 |
| ctacacgtta  | gatttgccgt  | accaatctct  | gaatgcccc   | taattattat | ttccagtgtt  | 1440 |
| tgggatgacc  | aggatcccaa  | gcctcctgct  | gccacaatgt  | ttataaaggc | caaataatga  | 1500 |
| cgggggctaa  | gttggtgctt  | ttgagaacca  | agtaaaacaa  | aaccactggg | aggagtctat  | 1560 |
| tttaaagaat  | tcggttgaaa  | aaaatagatc  | caatcagttt  | ataccctagt | tagtggtttg  | 1620 |
| cctcacctaa  | taggctggga  | gactgaagac  | tcagcccggg  | tggctgcaga | aaaatgattg  | 1680 |
| gccccagtc   | ccttgtttgt  | cccttctaca  | ggcatgagga  | atctgggagg | ccctgagaca  | 1740 |

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gggattgtgc  ttcattccaa  tctattgctt  caccatggcc  ttatgaggca  ggtgagagat  1800
gtttgaattt  ttctcttcct  tttagtattc  ttagttgttc  agttgccaa  gatccctgat  1860
cccatTTTTc  tctgacgtcc  acctcctacc  ccataggagt  tagaagttag  ggTTtaggca  1920
tcattttgag  aatgctgaca  ctttttcagg  gctgtgattg  agtgagggca  tgggtaaaaa  1980
tatttcttta  aaagaaggat  gaacaattat  atttatatTT  caggttatat  ccaatagtag  2040
agttggcttt  tttttttttt  ttttggtcat  agtgggtgga  tttgttgcca  tgtgcacctt  2100
gggggtttgt  aatgacagtG  ctaaaaaaaa  agcatttttt  ttttatgatt  tgtctctgtc  2160
acccttgtcc  ttgagtgtc  ttgctattaa  cgttatttgt  aatttagttt  gta  2213

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&lt;210&gt; 138

&lt;211&gt; 1508

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 138

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gagcgcggtt  accggacggg  ctgggtctat  ggTcgctccg  cgcccgctcc  gccgcgtggt  60
gcttttttat  cagggcaagc  tgtgttccat  ggcagggaac  ttttggcaga  gctccacta  120
tttgcaatgg  attttgata  aacaagatct  gttgaaggag  cgccaaaagg  atttaaagtt  180
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gtttttggca  tccaaagtag  aggaatttgg  agtagtttca  aatacaagat  tgattgctgc  420
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gatgaatcat  atattagaat  gtgaattcta  tctgttagaa  ctaatggatt  gttgcttgat  540
agtgtatcat  ccttatagac  ctttgctcca  gtatgtgcag  gacatgggcc  aagaagacat  600
gttgcttccc  cttgcatgga  ggatagtga  tgatacctac  agaacggatc  tttgcctact  660
gtatcctcct  ttcatgatag  ctttagcttg  cctacatgta  gctgtgttg  tacagcagaa  720
agatgccagg  caatggtttg  ctgagctttc  tgtggatatg  gaaaagattt  tggaaataat  780
caggggttatt  ttaaaactat  atgagcagtG  gaagaatttc  gatgagagaa  aagagatggc  840
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tccaaatgga  agtcagaact  ctagctacag  ccaatcttaa  aacattccga  agaattccat  960
agtggaccac  ttggaaataa  accattggac  agatttcagt  aatgtcttca  gtggaacaca  1020
aatgaaaatg  aatagcttgt  ttctgtcaag  catattggaa  agtgatttta  tttttgcaaa  1080
tagtttttct  ttaatatgat  tctagtacat  aattgattga  ttaaactctc  tgattataaa  1140
tgtttgga  ggTtctaagg  ggacctacag  acagacatac  atagacattt  caaaattaat  1200
agcttttgat  tagtataata  tttcttaatt  tggataataa  aaattgtagc  tttttattaa  1260
gccaggaaac  atgaagcata  atttgtttaa  aattctcttt  ggtcattgag  ggacccaaaa  1320
aggacgtaaa  atttacagtc  aatctatgag  ggTttttttc  cctccataag  tttaaacttta  1380
aaactgtatt  taaggaatca  aatcttacaa  aatcctggaa  gatttttggt  atgatgttga  1440
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gtttgagg  1508

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&lt;210&gt; 139

&lt;211&gt; 4320

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 139

```

aggatttggg  gtggaaggca  ggcattggtca  acccatgtca  ctgacaggag  agcagagaca  60
gacgtgtctc  tctccacgtc  ttccagccag  taaaagaagc  caagctggag  cccaaagcca  120
ggtgttctga  ctcccagcgt  ggggtccct  gcaccaacca  tgagccgcct  gctctggagg  180
aaggtggccg  gcgccaccgt  cgggccaggg  ccggttccag  ctccggggcg  ctgggtctcc  240
agctccgtcc  ccgcgtccga  cccagcgac  gggcagcggc  ggcggcagca  gcagcagcag  300
cagcagcagc  agcagcaaca  gcagcctcag  cagccgcaag  tgctatcctc  ggagggcggg  360
cagctgcggc  acaaccatt  ggacatccag  atgctctcga  gagggctgca  cgagcaaatc  420
ttcgggcaag  gaggggagat  gcctggcgag  gccgcgggtg  gccgcagcgt  cgagcacctg  480

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115/147

|             |            |             |             |             |             |      |
|-------------|------------|-------------|-------------|-------------|-------------|------|
| cagaagcacg  | ggctctgggg | gcagccagcc  | gtgcccttgc  | ccgacgtgga  | gctgcgcctg  | 540  |
| ccgcccctct  | acggggacaa | cctggaccag  | cacttccgcc  | tcctggccca  | gaagcagagc  | 600  |
| ctgccctacc  | tggaggcggc | caacttgctg  | ttgcaggccc  | agctgcccc   | gaagcccccg  | 660  |
| gcttgggcct  | gggcgagg   | ctggaccocg  | tacggccccg  | agggggaggc  | cgtaccocgtg | 720  |
| gccatccccg  | aggagcgggc | cctgggtgttc | gacgtggagg  | tctgcttggc  | agagggaaact | 780  |
| tgccccacat  | tggcggtggc | catatcccc   | tcggcctggt  | attcctggtg  | cagccagcgg  | 840  |
| ctggtggaag  | agcgttactc | ttggaccagc  | cagctgtcgc  | cggctgacct  | catccccctg  | 900  |
| gaggtcccta  | ctggtgccag | cagccccacc  | cagagagact  | ggcaggagca  | gttagtggtg  | 960  |
| gggcacaatg  | tttcctttga | ccgagctcat  | atcagggagc  | agtacctgat  | ccagggttcc  | 1020 |
| cgcattgcgtt | tcctggacac | catgagcatg  | cacatggcca  | tctcagggtc  | aagcagcttc  | 1080 |
| cagcgcagtc  | tgtggatagc | agccaagcag  | ggcaaacaca  | aggtccagcc  | ccccacaaag  | 1140 |
| caaggccaga  | agtcccagag | gaaagccaga  | agaggcccag  | cgatctcatc  | ctgggactgg  | 1200 |
| ctggacatca  | gcagtgtcaa | cagtctggca  | gaggtgcaca  | gactttatgt  | aggggggcoct | 1260 |
| cccttagaga  | aggagcctcg | agaactgttt  | gtgaagggca  | ccatgaagga  | cattcgtgag  | 1320 |
| aacttccagg  | acctgatgca | gtactgtgcc  | caggacgtgt  | gggccaccca  | tgagggttttc | 1380 |
| cagcagcagc  | taccgctctt | cttgagagag  | tgtccccacc  | cagtgactct  | ggccggcatg  | 1440 |
| ctggagatgg  | gtgtctccta | cctgcctgtc  | aaccagaact  | gggagcgta   | cctggcagag  | 1500 |
| gcacagggca  | cttatgagga | gctccagcgg  | gagatgaaga  | agtcgttgat  | ggatctggcc  | 1560 |
| aatgatgcct  | gccagctgct | ctcaggagag  | aggtacaaag  | aagaccctcg  | gctctgggac  | 1620 |
| ctggagtggg  | acctgaaga  | atttaagcag  | aagaaagcta  | agaaggtgaa  | gaaggaacca  | 1680 |
| gccacagcca  | gcaagttgcc | catcgagggg  | gctggggccc  | ctggtgatcc  | catggctcag  | 1740 |
| gaagacctcg  | gccccgtcag | tgaggaggag  | gagtttcaac  | aagatgtcat  | ggcccgogcc  | 1800 |
| tgcttgacga  | agctgaagg  | gaccacagag  | ctcctgcccc  | agcggcccca  | gcaccttcc   | 1860 |
| ggacaccctg  | gatggtaccg | gaagctctgc  | ccccggctag  | acgaccctgc  | atggacccccg | 1920 |
| ggccccagcc  | tcctcagcct | gcagatgcgg  | gtcacaccta  | aactcatggc  | acttacctgg  | 1980 |
| gatggcttcc  | ctctgcacta | ctcagagcgt  | catggctggg  | gctacttgg   | gcctggggcg  | 2040 |
| cgggacaacc  | tggccaagct | gcccagacgt  | accaccctgg  | agtcagctgg  | ggtggtctgc  | 2100 |
| ccctacagag  | ccatcgagtc | cctgtacagg  | aagcaactgtc | tcgaacagg   | gaagcagcag  | 2160 |
| ctgatgcccc  | aggagccgg  | cctggcggag  | gagttcctgc  | tactgacaa   | tagtgccata  | 2220 |
| tggcaaacgg  | tagaagaact | ggattactta  | gaagtggagg  | ctgaggccaa  | gatggagaac  | 2280 |
| ttgcgagctg  | cagtgccagg | tcaaccctta  | gctctgactg  | cccgtgggtg  | ccccaggac   | 2340 |
| accagcccca  | gctatcacca | tggcaatgga  | ccttacaacg  | acgtggacat  | ccctggctgc  | 2400 |
| tggttttttca | agctgectca | caaggatggt  | aatagctgta  | atgtgggaag  | cccccttgcc  | 2460 |
| aaggacttcc  | tgcccaagat | ggaggatggc  | accctgcagg  | ctggcccagg  | aggtgccagt  | 2520 |
| gggccccgctg | ctctggaaat | caacaaaatg  | atttctttct  | ggaggaaacgc | ccataaacgt  | 2580 |
| atcagctccc  | agatggtggt | gtggtgcgcc  | aggtcagctc  | tgccccgtgc  | tgtgatcagg  | 2640 |
| cacccccgact | atgatgagga | aggcctctat  | ggggccatcc  | tgccccaaat  | ggtgactgcc  | 2700 |
| ggcaccatca  | ctgcggggc  | tgtggagccc  | acatggctca  | ccgccagcaa  | tgccccggcct | 2760 |
| gaccgagtag  | gcagtgagtt | gaaagccatg  | gtgcaggccc  | cacctggcta  | cacctgtgtg  | 2820 |
| ggtgctgatg  | tggactccca | agagctgtgg  | attgcagctg  | tgcttgagga  | cgcccccttt  | 2880 |
| gccggcatgc  | atggctgcac | agcctttggg  | tggatgacac  | tgccaggcag  | gaagagcagg  | 2940 |
| ggcactgatc  | tacacagtaa | gacagccact  | actgtgggca  | tcagccgtga  | gcatgccaaa  | 3000 |
| atcttcaact  | acggccgcac | ctatggtgct  | gggcagccct  | ttgctgagcg  | cttactaatg  | 3060 |
| cagtttaacc  | accggctcac | acagcaggag  | gcagctgaga  | aggcccagca  | gatgtacgct  | 3120 |
| gccaccaagg  | gcctccgctg | gtatcggctg  | tcggatgagg  | gcgagtggct  | ggtgaggag   | 3180 |
| ttgaacctcc  | cagtggacag | gactgagggt  | ggctggattt  | ccctgcagga  | tctgcgcaag  | 3240 |
| gtccagagag  | aaactgcaag | gaagtcacag  | tggagaagat  | gggaggtgg   | tgctgaacgg  | 3300 |
| gcattggaag  | ggggcacaga | gtcagaaatg  | ttcaataagc  | ttgagagcat  | tgctacgtct  | 3360 |
| gacataccca  | gtacccgggt | gctgggtgc   | gagccctgga  | gagccctgga  | gccctggct   | 3420 |
| gtccaggaag  | agtttatgac | cagcctgtgt  | aattgggtgg  | tacagagctc  | tgctgttgac  | 3480 |
| tacttacacc  | tcattgctgt | ggccatgaag  | tggctgtttg  | aagagtttgc  | catagatggg  | 3540 |
| cgcttctgca  | tcagcatcca | tgacgaggtt  | cgctacctgg  | tgccgggagga | ggaccgctac  | 3600 |
| cgcgctgccc  | tggccttgca | gatcaccaac  | ctcttgacca  | ggtgcatgtt  | tgccatacag  | 3660 |
| ctgggtctga  | atgacttgcc | ccagtcagtc  | gcctttttca  | gtgcagtcga  | tattgaccgg  | 3720 |
| tgcctcagga  | aggaagtgc  | catggattgt  | aaaaccctt   | ccaaccacac  | tgggatggaa  | 3780 |
| aggagatacg  | ggattcccca | gggtgaagcg  | ctggatatatt | accagataat  | tgaactcacc  | 3840 |
| aaaggctcct  | tggaaaaacg | aagccagcct  | ggaccatagc  | actgcctgga  | ggctctgtat  | 3900 |
| ttgctcccgt  | ggagcttcat | cggggtgggt  | caggctccca  | aactcagggt  | ttcagctgtg  | 3960 |

116/147

|            |            |            |            |            |            |      |
|------------|------------|------------|------------|------------|------------|------|
| ctttttgcaa | aagggttgc  | taaggccagc | catttttcag | tagcaggacc | tgccaagaag | 4020 |
| attccttcta | actgaagtg  | cagttgaatt | cagtgggttc | agaaccaaga | tgccaacatc | 4080 |
| ggtgtggact | acaggacaag | gggcattgtt | gcttggtggg | taaaaatgaa | gcagaagccc | 4140 |
| caaagttcac | attaactcag | gcatttcatt | tattttttcc | ttttcttctt | ggctggttct | 4200 |
| ttgttctgtc | ccccatgtc  | tgatgcagtg | ccctagaagg | ggaaagaatt | aatgctctaa | 4260 |
| cgtgataaac | ctgctccaag | gcagtggaaa | taaaaagaag | gaaaaaaaaa | aaaaaaaaaa | 4320 |

&lt;210&gt; 140

&lt;211&gt; 2245

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 140

|            |             |            |            |             |             |      |
|------------|-------------|------------|------------|-------------|-------------|------|
| ggagcaagag | gtggttgggg  | ggggaccatg | gctgacgttt | tcccggggcaa | cgactccacg  | 60   |
| gcgtctcagg | acgtggccaa  | ccgcttcgcc | cgcaaagggg | cgctgaggca  | gaagaacgtg  | 120  |
| cacgaggtga | aggaccacaa  | attcatcgcg | cgcttcttca | agcagcccac  | cttctgcagc  | 180  |
| cactgcaccg | acttcatctg  | ggggtttggg | aaacaaggct | tccagtgcc   | agtttgctgt  | 240  |
| tttgtgttcc | acaagaggtg  | ccatgaattt | gttacttttt | cttgctccggg | tgccgataag  | 300  |
| ggaccgcaca | ctgatgacct  | caggagcaag | cacaagttca | aaatccacac  | ttacgggaagc | 360  |
| cccaccttct | gcgatcactg  | tgggtcactg | ctctatggac | ttatccatca  | agggatgaaa  | 420  |
| tgtgacacct | gcgatatgaa  | cgttcacaa  | caatgcgtca | tcaatgtccc  | cagcctctgc  | 480  |
| ggaatggatc | acactgagaa  | gagggggcgg | atttacctaa | aggctgaggt  | tgctgatgaa  | 540  |
| aagctccatg | tcacagtacg  | agatgcaaaa | aatctaattc | ctatggatcc  | aaacgggctt  | 600  |
| tcagatcctt | atgtgaagct  | gaaacttatt | cctgatccca | agaatgaaag  | caagcaaaaa  | 660  |
| acaaaaacca | tccgctccac  | actaaatccg | cagtggaatg | agtcctttac  | attcaaatgt  | 720  |
| aaaccttcag | acaaagaccg  | acgactgtct | gtagaaatct | gggactggga  | tcgaacaaca  | 780  |
| aggaatgact | tcattgggatc | cctttccttt | ggagtttcgg | agctgatgaa  | gatgccggcc  | 840  |
| agtggatggt | acaagtgtgt  | taaccaagaa | gaaggtgagt | actacaacgt  | acccattccg  | 900  |
| gaaggggacg | aggaaggaaa  | catggaactc | aggcagaaat | tcgagaaagc  | caaacttggc  | 960  |
| cctgctggca | acaaagtcac  | cagtccctct | gaagacagga | aacaaccttc  | caacaacctt  | 1020 |
| gaccgagtga | aactcacgga  | cttcaatttc | ctcatggtgt | tgggaaagg   | gagttttgga  | 1080 |
| aaggtgatgc | ttgccgacag  | gaagggcaca | gaagaactgt | atgcaatcaa  | aatcctgaag  | 1140 |
| aaggatgtgg | tgattcagga  | tgatgacgtg | gagtgcacca | tggtagaaaa  | gcgagtcctg  | 1200 |
| gcctgcttg  | acaaaacccc  | gttcttgacg | cagctgcact | cctgcttcca  | gacagtggat  | 1260 |
| cggtgtact  | tcgtcatgga  | atatgtcaac | ggtggggacc | tcatgtacca  | cattcagcaa  | 1320 |
| gtaggaaaat | ttaaggaacc  | acaagcagta | ttctatgcgg | cagagatttc  | catcggattg  | 1380 |
| ttctttcttc | ataaaagagg  | aatcatttat | agggatctga | agttagataa  | cgatcatgtt  | 1440 |
| gattcagaag | gacatatcaa  | aattgctgac | tttgggatgt | gcaaggaaaca | catgatggat  | 1500 |
| ggagtcacga | ccaggacctt  | ctgtgggact | ccagattata | tcgccccaga  | gataatcgct  | 1560 |
| tatcagccgt | atggaaaatc  | tgtggactgg | tgggcctatg | gcgtcctgtt  | gtatgaaatg  | 1620 |
| cttgccgggc | agcctccatt  | tgatggtgaa | gatgaagacg | agctatttca  | gtctatcatg  | 1680 |
| gagcacaacg | tttcctatcc  | aaaatccttg | tccaaggagg | ctgtttctat  | ctgcaaagga  | 1740 |
| ctgatgacca | aacacccagc  | caagcggctg | ggctgtgggc | ctgaggggga  | gagggacgtg  | 1800 |
| agagagcatg | ccttcttccg  | gaggatcgac | tgggaaaaac | tggagaacag  | ggagatccag  | 1860 |
| ccaccattca | agcccaaagt  | gtgtggcaaa | ggagcagaga | actttgacaa  | gttcttcaca  | 1920 |
| cgaggacagc | ccgtcttaac  | accacctgat | cagctggtta | ttgctaacat  | agaccagtct  | 1980 |
| gattttgaag | ggttctcgta  | tgtcaacccc | cagtttgctg | accccatctt  | acagagtgca  | 2040 |
| gtatgaaact | caccagcgag  | aacaaacacc | tccccagccc | ccagccctcc  | ccgcagtgga  | 2100 |
| agtgaatcct | taaccctaaa  | attttaaggc | cacggcttgt | gtctgattcc  | atatggaggc  | 2160 |
| ctgaaaattg | tagggttatt  | agtccaaatg | tgatcaactg | ttcaggggtct | ctctcttaca  | 2220 |
| accaagaaca | ttatcttagt  | ggaag      |            |             |             | 2245 |

&lt;210&gt; 141

&lt;211&gt; 1362

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

117/147

&lt;400&gt; 141

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catttgggga cgctctcagc tctcggcgca cggcccagct tccttcaaaa tgtctactgt 60
tcacgaaatc ctgtgcaagc tcagcttgga gggatgatcac tctacacccc caagtgcata 120
tggtgtctgtc aaagcctata ctaactttga tgctgagcgg gatgctttga acattgaaac 180
agccatcaag accaaagggtg tggatgaggt caccattgtc aacattttga ccaaccgcag 240
caatgcacag agacaggata ttgccttcgc ctaccagaga aggacccaaa aggaacttgc 300
atcagcactg aagtcagcct tatctggcca cctggagacg gtgattttgg gcctattgaa 360
gacacctgct cagtatgacg cttctgagct aaaagcttcc atgaaggggc tgggaaccga 420
cgaggactct ctcatatgaga tcatctgctc cagaaccaac caggagctgc aggaaattaa 480
cagagtctac aaggaaatgt acaagactga tctggagaag gacattattt cggacacatc 540
tggtgacttc cgcaagctga tggttgccct ggcaaagggt agaagagcag aggatggctc 600
tgtcattgat tatgaactga ttgaccaaga tgctcgggat ctctatgacg ctggagtga 660
gaggaaagga actgatgttc ccaagtggat cagcatcatg accgagcggg gcgtgcccc 720
cctccagaaa gtatttgata ggtacaagag ttacagccct tatgacatgt tggaaagcat 780
caggaaagag gttaaaggag acctggaaaa tgctttcctg aacctgggtc agtgcattca 840
gaacaagccc ctgtattttg ctgatcggct gtatgactcc atgaagggca aggggacgcg 900
agataaggtc ctgatcagaa tcatggcttc ccgcagtga gtggacatgt tgaaaattag 960
gtctgaattc aagagaaagt acggcaagtc cctgtactat tatatccagc aagacactaa 1020
ggcgactac cagaaaagcgc tgctgtacct gtgtgggtga gatgactgaa gcccagacag 1080
gcctgagcgt ccagaaatgg tgctcaccat gcttccagct aacagggtcta gaaaaccagc 1140
ttgcgaataa cagtccccgt ggccatccct gtgaggggtga cgttagcatt acccccaacc 1200
tcattttagt tgctaagca ttgcctggcc ttctgtctta gtctctctg taagccaaag 1260
aaatgaacat tccaaggagt tggaagtga gtctatgatg tgaaacactt tgccctcctgt 1320
gtactgtgtc ataaacagat gaataaactg aatttgtact tt 1362

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&lt;210&gt; 142

&lt;211&gt; 1137

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 142

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aagagcgagt cttggcctta gcgcgggctt tgcctccctg cttgccacgt ccagacatag 60
cgagcgcaac tcaactacgag caaccacaaa gtgaacggga aaggcggcgc tttttataaa 120
cactattggg cgcgaaaaag aagacgtgtt gttggttagg gctgcagttt aatttcaacc 180
aatagtagtg cgtcttcttg atttgcaaat cctgattggg cagacctgac ctctgacgtt 240
accctgaata actaccaatc agacacaaga cttcaactct tcaccttatt tgcataagcg 300
attctatata aaagcgctt gtcataccct gctcacgctg tttttccttt tcgttggcgc 360
tttatagcta cacagtgtca tgccagagcc agcgaagtct gctccgccc cgaaaaagg 420
ctccaagaag gcggtgacta aggcgcagaa gaaagacggc aagaagcgca agcgcagccg 480
caaggagagc tattccatct atgtgtacaa ggttctgaag cagggtccacc ctgacaccgg 540
catttcgtcc aaggccatgg gcatcatgaa ttcgtttgtg aacgacattt tcgagcgcac 600
cgcaggtgag gcttcccgcc tggcgcatta caacaagcgc tcgaccatca cctccaggga 660
gatccagacg gccgtgcgcc tgctgctgcc tggggagtgt gccaaagcag ccgtgtccga 720
gggtactaag gccgtcacca agtacaccag cgctaagtaa acagtgaagt ggttgcaaac 780
tctcaacctt aacggctctt ttaagagcca cccatgttct caaagaaaga gctgggtgctt 840
gtattcctcc tctgtggcc actgacaaac cctgtgaact tgctactgtg ttttttggtc 900
tgaagtagag cagttattta actaatcctt agtgactttt tttttttaga tctgacattc 960
taatcttaga gttaagtaag gagatgggaa attttctatt ataagttcga aaccaattaa 1020
aatacgttag aaaccaatta aaatactcgt cgggtccccc tcggtttagt atttggaaca 1080
gtgccaaagt gcagcggttg tcagtttgaa tttgcccggg caacgcccgc ccttcct 1137

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&lt;210&gt; 143

&lt;211&gt; 1270

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

118/147

&lt;400&gt; 143

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agacgttcgc acacctgggt gccagcgccc cagaggtccc gggacagccc gaggcgcgcg 60
gcccgcgcgc ccgagotccc caagccttcg agagcggcgc acaactcccg tctccactcg 120
ctcttccaac acccgctcgt tttggcggca gctcgtgtcc cagagaccga gttgccccag 180
agaccgagac gccgcgcgtg cgaaggacca atgagagccc cgctgctacc gccggcgccg 240
gtgggtgctgt cgctcttgat actcggctca ggccattatg ctgctggatt ggacctcaat 300
gacacctact ctgggaagcg tgaaccattt tctggggacc acagtgtctga tggatttgag 360
gttacctcaa gaagtgaagt gtcttcaggg agtgagattt cccctgtgag tgaaatgcct 420
tctagtagtg aaccgtcctc gggagccgac tatgactact cagaagagta tgataacgaa 480
ccacaaatag ctggctatat tgtcgatgat tcagtcagag ttgaacaggt agttaagccc 540
ccccaaaaca agacggaaag tgaaaatact tcagataaac caaaagaaa gaaaaaggga 600
ggcaaaaatg gaaaaaatag aagaaacaga aagaagaaaa atccatgtaa tgcagaattt 660
caaaatttct gcattcacgg agaatgcaaa tatatagagc acctggaagc agtaacatgc 720
aaatgtcagc aagaatattt cggatgaacg tgtggggaaa agtccatgaa aactcacagc 780
atgattgaca gtatgtttatc aaaaattgca ttagcagcca tagctgcctt tatgtctgct 840
gtgatcctca cagctgttgc tgttattaca gtccagctta gaagacaata cgtcaggaaa 900
tatgaaggag aagctgagga acgaaagaaa cttcgacaag agaatggaaa tgtacatgct 960
atagcataac tgaagataaa attacaggat atcacattgg agtcaactgcc aagtcatagc 1020
cataaattgat gagtcgggtcc tctttccagt ggatcataag acaatggacc ctttttgtaa 1080
tgatggtttt aaactttcaa ttgtcacttt ttatgctatt tctgtatata aagggtgcacg 1140
aaggtaaaaa gtattttttc aagttgtaaa taattttatt aatatttaat ggaagtgtat 1200
ttatttttaca gctcattaaa cttttttaac caaacagaaa aaaaaaaaaa aaaaaaaaaa 1260
aaaaaaaaaa                                     1270

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&lt;210&gt; 144

&lt;211&gt; 3953

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 144

```

ttatggttaa tgttcttata gacatccaaa ggtcagaaac tattccatt tgaaaaatat 60
ctgttggtgt ataaatgtgc tgttttcttt cctcttctcc ctgacttttag ggaactgctc 120
gcagaaagaa gaaggtgggt catagaacag ccacagcaga tgacaaaaaa cttcagttct 180
ccttaaagaa gttaggggta aacaatatct ctgggtattga agaggcaagt atcaaatatt 240
gttactttta aaaacaagat ttggctggga aaagttaacg ttaatgcatt aaatgggttg 300
ttgggttttt ttttaacttag ggacttcaaa gtccctaaga tgtgtttcta ccataaatta 360
ataaatatca gggagctcat taagtctgaa tgctattaga atacatattc cattccaggc 420
aaaatttcac ctgtgcttac acgtgaaata ctagttagcc agagctagtt taataaaaca 480
tttgttttta aagagactgg tcagcattgc taatttaaat ttttcttttc ttaatagggt 540
aatatgttta caaaccaagg aacagtgatc cactttaaca accctaaagt tcaggcatct 600
ctggcagcga acactttcac cattacaggc catgctgaga caaagcagct gacagaaatg 660
ctaccagca tcttaaaacca gcttggtgcg gatagtctga ctagttaaag gagactggcc 720
gaagctctgc ccaaacaatg tgagtttcct agtaatggtt ttaccaggga attactcatt 780
tagcagctga tttctgatct cagggctcag aatggatatg agtattttta agtttggaag 840
tgcaagcttt aaaaataaca gatttgtaac tgattttaag caactgtcct tgctcaagtt 900
tgcatgaatt gatgtagcgt gccatgattg ttacacttga ttttggtgaa tgttttctac 960
ttacttgatt tggatcagat acttttatta actagaaatg atgaaaatgt taatttggtg 1020
ctttgccaat aactacttgt aagtttgga ttgaaaaaaa aattagtgtt aattatgaaa 1080
ttacttcagt ttcacttata tagttcgtat taccagtaat cttttaaaaa tggcttgcca 1140
gtattctggc attttaatta cagtgtgata gggatttatt cggggcagaa aatagtgtag 1200
ctgaatatac atctgaggat gtggcagtgt tatgctgttt tctgtgctta aaattttgaa 1260
gaataggaat gcaggaggaa gtcagaggct tatatatggc tcttttagtta cccatgtttt 1320
tctaggtatt gacttaactc gcctcaattt tcatttttat tatcacattg agttgcaggt 1380
tctaaactgt cagggctttc agagctgaaa taggcttttg aagtatccca ctgatgcctg 1440
tatgggccta gtacataact ctctgtgta cgttcatatt cttgtgtgat aaaggagagt 1500
ggatgcttac cactcacaga ctctttaatt tttttacttt aacttttttc atttcagtaa 1560

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119/147

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gtggttggtg agcatcacc ttatgccaca cacagagtag ttgagaaaat ggcattctca 1620
tttgtctccc aaaatctcac catgatttgg tatgtgggtt ttacctgcac tctaagagtt 1680
ccctactgcc cttatactac ctcaggccta tgggtggccag aggattgaaa gagtggtagt 1740
gaatttggtt gttggcggtt ctagtatatt aaccatttgg tagacattag aatatcatgt 1800
tattgatagt atcataggat aaaatcccaa atgtccctta tcatggaaat aagttgtaac 1860
aacacttggc atttcatctg ttcttttttt tttttttttt ttttttttgg tgaatattta 1920
ttaaaaacct agacaaataa tgtttacatt ttcttttcat agctgtggat ggaaaagcac 1980
cacttgctac tggagaggat gatgatgatg aagttccagg taggaacggt tgcttgtggt 2040
taacctagag aatcttagcc aagggagaat aagaaatctt tgtaggaaaa actaccagg 2100
gaagaggggt ggtaagttaa gatggacata gatcttactt agaattgagaa aaataatgca 2160
gtattaggtt attgagaatt atgtttatag acttgacttg gcttgtttct gtttgggatc 2220
ccaaggatgt gtaggtatct aaccttaaat attgaataaa taagtatata tatatagtac 2280
cctaaatata actattacct gcagagcact aatgaccctt gctccctact ttgaaactca 2340
tgaatttaca agaaggtgtg gagttgttca ggtatcttgg gatatatata tgcattctaa 2400
aatctgtagc agcataactc cttttgggaa tcagaggatt ttgtctctta cctgttattg 2460
gataaattta cgttcttcta aaatatattat tgggcaggag aatcactgga ctcataaata 2520
ttcccacttt gcatagacag gtatccttag gaatcaggaa aattttaaca ttgtgtgtca 2580
ttgtattctt tggttctgct cccccactat tgaccaatgt agagatggga agaggggggc 2640
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tcatcattgg caaatgaatg ctctttcctt catccccttt taatatctga taattatttg 2760
tagattggct tttttaagaa tttctactct tttcttttct ctagatcttg tggagaattt 2820
tgatgaggct tccaagaatg aggcaaactg aattgagtca acttctgaag ataaaaacct 2880
aagaagttta ctgggagctg ctattttata ttatgactgc tttttaagaa aatttttgtt 2940
tatggatctg ataaaatcta gatctcta atttttaagc ccaagcccct tggacactgc 3000
agctcttttc agtttttgct tatacacaat tcattctttg cagctaatta agccgaagaa 3060
gcctgggaat caagtttgaa acaaagatta ataaagttct tttgcctagt atacagtttt 3120
atttttttat ttattgacac cgatctgtac acagtaaaaa aaattgotta tagaaaagcta 3180
atcatggcat gtaatatggc tgataacctt tgggaatttg ttaaagattt aaaatcacgg 3240
tgtaagtgtt acaaagggtg tataaagttc tcaggtttga aaactttgtc tccaacagtc 3300
cttagtgctt ccattgattta tatggtgggt gtaaatatga gaattagatga ttccttagtg 3360
gataaacaga catttctccc tgatattctc tattgtgaagc atatgttaag tgccttttat 3420
gaattacctt cgggtgttatc ttcttttatt cctcaatttg tgaagaacta atagctccat 3480
ttttagatag taacctgagg tttagaactt ctaaaaagta aaagtaatct ccagatccct 3540
tctttgtagg atattttata aggtgacttg gaaaaggtag tgtttagaat aggagtggct 3600
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atttaataaa aaatatacag taaaattgag catatacagt taaaagaatt tataatgtct 3720
gccactataa ccaggcttac cagacagttt catgggtccag aaaatcccta aacatagggt 3780
tacttttaaa cattttacaa attacaatga aacaattgtg taatctgaac caaggccatt 3840
tgaggagaaa tagttctact tgtatggtat ttatttttaa atttttcata gcaatttgca 3900
agtacctttt gaaagtatta tcagttgtat ctaaaatgca ctattaaccg tgg 3953

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&lt;210&gt; 145

&lt;211&gt; 3213

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 145

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atgtgcttca gtttcataat gcctcctgct atggcagaca tccttgacat ctgggcgggtg 60
gattcacaga tagcatctga tggctccata cctgtggatt tccttttgcc cactgggatt 120
tatatccagt tggaggtacc tcgggaagct accatttctt atattaagca gatgttatgg 180
aagcaagttc acaattacc aatgttcaac ctccttatgg atattgactc ctatatgttt 240
gcatgtgtga atcagactgc tgtatatgag gagcttgaag atgaaacacg aagactctgt 300
gatgtcagac cttttcttcc agttctcaaa ttagtgacaa gaagttgtga cccaggggaa 360
aaattagact caaaaattgg agtccttata ggaaaagggtc tgcattgaatt tgattccttg 420
aaggatcctg aagtaaatga atttcgaaga aaaatgcgca aattcagcga ggaaaaaatc 480
ctgtcacttg tgggtgtgct ttggatggac tggctaaaac aaacatatcc accagagcat 540
gaaccatcca tccctgaaaa cttagaagat aaactttatg ggggaaagct catcgtagct 600

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120/147

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gttcattttg aaaactgcc a ggacgtgttt agctttcaag tgtctcctaa tatgaatcct 660
atcaaagtaa atgaattggc aatccaaaaa cgtttgacta ttcattggga ggaagatgaa 720
gttagccctt atgattatgt gttgcaagtc agcgggagag tagaatatgt ttttggtgat 780
catccactaa ttcagttcca gtatatccgg aactgtgtga tgaacagagc cctgccccat 840
tttatacttg tggaatgctg caagatcaag aaaatgtatg aacaagaaat gattgccata 900
gaggctgcca taaatcgaaa ttcattctaat ctctctcttc cattaccacc aaagaaaaca 960
cgaattatatt ctcattgtttg ggaaaaataac aaccctttcc aaattgtctt ggtaagggga 1020
aataaactta acacagagga aactgtaaaa gtcatgtca gggctgggtct ttttcatggt 1080
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tggaatgaac cactggaatt tgatattaat atttgtgact taccaagaat ggctcgatta 1200
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caactggtgc aagtgttaaa atatgagcct tttcttgatt gtgcccctct tagattccta 1980
ttagaaagag cacttggtaa tcggaggata gggcagtttc tattttggca tcttaggtca 2040
gaagtgcaca ttcctgctgt ctacgtacaa tttggtgtca tccttgaagc atactgccgg 2100
ggaagtgtgg ggcacatgaa agtgctttct aagcaggttg aagcactcaa taagttaaaa 2160
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gccatgcata cctgttttaa acagagtgtc taccgggaag ccctctctga cctgcagtca 2280
cccctgaacc catgtgttat cctctcagaa ctctatgttg aaaagtgcaa atacatggat 2340
tccaaaatga agcctttgtg gctggtatag aataacaagg tatttgggtga ggattcagtt 2400
ggagtgattt ttaaaaatgg tgatgattta cgacaggata tgttgacact ccaaagtgtg 2460
cgcttgatgg atttactctg gaaagaagct ggtttgatc ttccggatgtt gccttatggc 2520
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catagtgcac acatcatggt caaaaaaact ggccagctct tccacattga ctttggacat 2820
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acctatgatt tcatccatgt cattcaacaa ggaaaaacag gaaatacaga aaagtttggc 2940
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atcactctct ttgcgtgat gttgactgca gggcttctct aactcacatc agtcaaagat 3060
atacagtatc ttaaggactc tcttgcatga gggaagagt aagaagaagc actcaaacag 3120
tttaagcaaa aatttgatga ggcgctcagg gaaagctgga ctactaaagt gaactggatg 3180
gccacacag ttcggaaaga ctacagatct taa 3213

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&lt;210&gt; 146

&lt;211&gt; 2602

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 146

```

gccgtgtcgc caccatggct ccgcaccgcc ccgcgccgcg gctgctttgc gcgctgtccc 60
tgccgctgtg cgcgctgtcg ctgcccgctc gcgcggccac tgcgtcgcgg ggggctccc 120
aggcgggggc gccccagggg cgggtgcccc aggcgcggcc caacagcatg gtgggtggaac 180
accccagatt cctcaaggca gggaaggagc ctggcctgca gatctggcgt gtggagaagt 240
tcgatctggg gcccggtgcc accaaccttt atggagactt cttcacgggc gacgcctacg 300
tcactcctgaa gacagtgcag ctgaggaaacg gaaatctgca gtatgacctc cactactggc 360

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121/147

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| tgggcaatga  | gtgcagccag  | gatgagagcg  | gggcgccgc   | catctttacc  | gtgcagctgg  | 420  |
| atgactacct  | gaacggccgg  | gccgtgcagc  | accgtgaggt  | ccagggcttc  | gagtcggcca  | 480  |
| ccttcctagg  | ctacttcaag  | tctggcctga  | agtacaagaa  | aggaggtgtg  | gcacaggat   | 540  |
| tcaagcacgt  | ggtacccaac  | gaggtggtgg  | tgcagagact  | cttcagggtc  | aaagggcggc  | 600  |
| gtgtgggtccg | tgccaccgag  | gtacctgtgt  | cctgggagag  | cttcaacaat  | ggcgactgct  | 660  |
| tcatcctgga  | cctgggcaac  | aacatccacc  | agtgggtgtg  | ttccaacagc  | aatcggtatg  | 720  |
| aaagactgaa  | ggccacacag  | gtgtccaagg  | gcacccggga  | caacgagcgg  | agtggccggg  | 780  |
| cccgagtgca  | cgtgtctgag  | gagggcactg  | agcccagggc  | gatgctccag  | gtgctggggc  | 840  |
| ccaagccggc  | tctgcctgca  | ggtaccgagg  | acaccgccaa  | ggaggatgcg  | gccaaccgca  | 900  |
| agctggccaa  | gctctacaag  | gtctccaatg  | gtgcagggac  | catgtccgtc  | tcctctgtgg  | 960  |
| ctgatgagaa  | ccccttcgcc  | cagggggccc  | tgaagtcaga  | ggactgcttc  | atcctggacc  | 1020 |
| acggcaaaga  | tgggaaaatc  | tttgtctgga  | aaggcaagca  | ggcaaacacg  | gaggagagga  | 1080 |
| aggctgccct  | caaaacagcc  | tctgacttca  | tcaccaagat  | ggactacccc  | aagcagactc  | 1140 |
| aggtctcggt  | ccttcctgag  | ggcgggtgaga | ccccactggt  | caagcagttc  | ttcaagaact  | 1200 |
| ggcgggaccc  | agaccagaca  | gatggcctgg  | gcttgtccta  | cctttccagc  | catatcgcca  | 1260 |
| acgtggagcg  | ggtgcccttc  | gacgccgcca  | ccctgcacac  | ctccactgcc  | atggccgccc  | 1320 |
| agcacggcat  | ggatgacgat  | ggcacaggcc  | agaaacagat  | ctggagaatc  | gaaggttcca  | 1380 |
| acaaggtgcc  | cgtggaccct  | gccacatatg  | gacagttcta  | tggaggcgac  | agctacatca  | 1440 |
| ttctgtacaa  | ctaccgccat  | ggtggccgcc  | aggggcagat  | aatctataac  | tggcaggggtg | 1500 |
| cccagtctac  | ccaggatgag  | gtcgctgcat  | ctgccatcct  | gactgctcag  | ctggatgagg  | 1560 |
| agctgggagg  | taccctgtgc  | cagagccgtg  | tgttccaagg  | caaggagccc  | gccacctca   | 1620 |
| tgagcctggt  | tgggtgggaag | cccatgatca  | tctacaaggg  | cggcacctcc  | cgcgaggcgc  | 1680 |
| ggcagacagc  | ccctgccagc  | acccgcctct  | tccagggtccg | cgccaacagc  | gctggagcca  | 1740 |
| cccgggctgt  | tgagggtattg | cctaaggctg  | gtgactgaa   | ctccaacgat  | gcctttgttc  | 1800 |
| tgaaaacccc  | ctcagccgcc  | tacctgtggg  | tgggtacagg  | agccagcgag  | gcagagaaga  | 1860 |
| cgggggcccc  | ggagctgctc  | agggtgctgc  | gggccaacc   | tgtgcagggtg | gcagaaggca  | 1920 |
| gcgagccaga  | tggottcttg  | gaggccctgg  | gcgggaaggc  | tgcctaccgc  | acatccccac  | 1980 |
| ggctgaagga  | caagaagatg  | gatgcccac   | ctcctgcct   | ccttgccctgc | tccaacaaga  | 2040 |
| ttggacgttt  | tgtgatcgaa  | gaggttctgt  | gtgagctcat  | gcaggaagac  | ctggcaacgg  | 2100 |
| atgacgtcat  | gcttctggag  | acctgggacc  | aggtccttgt  | ctgggttgga  | aaggattctc  | 2160 |
| aagaagaaga  | aaagacagaa  | gccttgactt  | gtgctaagcg  | gtacatcgag  | acggaccag   | 2220 |
| ccaatcggga  | tggcgggacg  | cccatcaccg  | tgggtgaagca | aggctttgag  | cctccctcct  | 2280 |
| ttgtgggctg  | gttccttggc  | tgggatgatg  | attactggtc  | tgtggacccc  | ttggacaggg  | 2340 |
| ccatggctga  | gctggctgcc  | tgaggagggg  | cagggccac   | ccatgtcacc  | ggtcagtgcc  | 2400 |
| ttttggaact  | gtccttccct  | caaagaggcc  | ttagagcgag  | cagagcagct  | ctgctatgag  | 2460 |
| tgtgtgtgtg  | tgtgtgtgtt  | gtttcttttt  | ttttttttta  | cagtatccaa  | aaatagccct  | 2520 |
| gcaaaaattc  | agagtccttg  | caaaattgtc  | taaaatgtca  | gtgtttggga  | aattaaatcc  | 2580 |
| aataaaaaca  | ttttgaagtg  | tg          |             |             |             | 2602 |

&lt;210&gt; 147

&lt;211&gt; 6480

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 147

|            |            |            |            |             |             |     |
|------------|------------|------------|------------|-------------|-------------|-----|
| agagcgagca | ggggagagcg | agaccagttt | taaggggagg | accggtgcga  | gtgaggcagc  | 60  |
| cccagggtc  | tgctcgccca | ccaccaatc  | ctcgctccc  | ttctgctcca  | ccttctctct  | 120 |
| ctgccctcac | ctctccccc  | aaaaccccct | atttagccaa | aggaaggagg  | tcaggggaac  | 180 |
| gctctccct  | ccccttccaa | aaaacaaaaa | cagaaaaacc | cttttccagg  | ccggggaaaag | 240 |
| caggagggag | aggggccgcc | gggctggcca | tggagctgct | gtgccacgag  | gtggaccccg  | 300 |
| tccgcagggc | cgtgcgggac | cgcaacctgc | tccgagacga | ccgcgtcctg  | cagaacctgc  | 360 |
| tcaccatcga | ggagcgctac | cttcgcgagt | gctcctactt | caagtgcgtg  | cagaaggaca  | 420 |
| tccaacccta | catgcgcaga | atggtggcca | cctggatgct | ggaggctctgt | gaggaacaga  | 480 |
| agtgcgaaga | agaggtcttc | cctctggcca | tgaattacct | ggaccgtttc  | ttggctgggg  | 540 |
| tcccgaactc | gaagtcccat | ctgcaactcc | tgggtgctgt | ctgcatgttc  | ctggcctcca  | 600 |
| aactcaaaga | gaccagcccg | ctgaccgcgg | agaagctgtg | catttacacc  | gacaactcca  | 660 |
| tcaagcctca | ggagctgctg | gagtgggaac | tgggtggtgt | ggggaagttg  | aagtgggaacc | 720 |

122/147

|            |             |             |             |             |             |      |
|------------|-------------|-------------|-------------|-------------|-------------|------|
| tggcagctgt | cactcctcat  | gacttcattg  | agcacatctt  | gcgcaagctg  | ccccagcagc  | 780  |
| gggagaagct | gtctctgac   | cgcaagcatg  | ctcagacctt  | cattgctctg  | tgtgccaccg  | 840  |
| actttaagtt | tgccatgtac  | ccaccgtcga  | tgatcgcaac  | tggaagtgtg  | ggagcagcca  | 900  |
| tctgtgggct | ccagcaggat  | gaggaagtga  | gctcgctcac  | ttgtgatgcc  | ctgactgagc  | 960  |
| tgctggctaa | gatcaccaac  | acagacgtgg  | attgtctcaa  | agcttgccag  | gagcagattg  | 1020 |
| aggcggtgct | cctcaatagc  | ctgcagcagt  | accgtcagga  | ccaacgtgac  | ggatccaagt  | 1080 |
| cggaggatga | actggacca   | gccagcaccc  | ctacagacgt  | gcgggatata  | gacctgtgag  | 1140 |
| gatgccagtt | gggcccgaag  | agagagacgc  | gtccataatc  | tgggtctcttc | ttctttctgg  | 1200 |
| ttgtttttgt | tctttgtgtt  | ttagggtgaa  | acttaaaaaa  | aaaattctgc  | ccccacctag  | 1260 |
| atcatattta | aagatctttt  | agaagtgaga  | gaaaaaggct  | ctacgaaaac  | ggaataataa  | 1320 |
| aaagcatttg | gtgcctattt  | gaagtacagc  | ataagggaat  | cccttgata   | tgcgaaacagt | 1380 |
| tattgtttga | ttatgtaaaa  | gtaatagtaa  | aatgcttaca  | ggaaaacctg  | cagagtattt  | 1440 |
| agagaatatg | tatgcctgca  | atatgggaac  | aaattagagg  | agactttttt  | ttttcatgtt  | 1500 |
| atgagctagc | acatacaccc  | ccttgtagta  | taattttcaag | gaactgtgta  | cgccatttat  | 1560 |
| ggcatgatta | gattgcaaag  | caatgaactc  | aagaaggaa   | tgaataaagg  | agggacatga  | 1620 |
| tggggaagga | gtacaaaaca  | atctctcaac  | atgattgaac  | catttgggat  | ggagaagcac  | 1680 |
| ctttgctctc | agccacctgt  | tactaagtca  | ggagtgtagt  | tggatctcta  | cattaatgtc  | 1740 |
| ctcttgctgt | ctacagtagc  | tgtacctaa   | aaaaagatgt  | tttattttgc  | cagttggaca  | 1800 |
| caggtgattg | gctcctgggt  | ttcatgttct  | gtgacatcct  | gcttcttctt  | ccaaatgcag  | 1860 |
| ttcattgcag | acaccacat   | attgctatct  | aatggggaaa  | tgtagctatg  | ggccataacc  | 1920 |
| aaaactcaca | tgaaacggag  | gcagatggag  | accaagggtg  | ggatccagaa  | tggagtcttt  | 1980 |
| tctgttattg | tattttaaag  | ggtaatgtgg  | ccttggcatt  | tcttcttaga  | aaaaactaa   | 2040 |
| tttttgggtg | tgattggcat  | gtctggttca  | cagtttagca  | ttgttataaa  | ccattccatt  | 2100 |
| cgaaaagcac | tttgaaaaat  | tgttcccag   | cgatagatgg  | gatggtttat  | gcaagtcag   | 2160 |
| ctgaatactc | ctccccctt   | ctcttttgcc  | ccctcccttc  | ctgccccag   | tctgggttac  | 2220 |
| tcttcgcttc | tggatatctg  | cgttctttgg  | tacacagttc  | tgggtgttct  | accaggactc  | 2280 |
| aagagacacc | ccttcctgct  | gacattccca  | tcacaacatt  | cctcagacaa  | gcctgtaaac  | 2340 |
| taaaatctgt | taccattctg  | atggcacaga  | aggatcttaa  | ttcccatctc  | tatacttctc  | 2400 |
| ctttggacat | ggaaagaaaa  | gttattgctg  | gtgcaaagat  | agatggctga  | acatcagggt  | 2460 |
| gtggcatttt | gttccctttt  | cogttttttt  | tttttttatt  | gttgttggtt  | attttattgc  | 2520 |
| aaagttgtat | tcagcgtaact | tgaatttttt  | ttcctctcca  | cttcttagag  | gcattcagtt  | 2580 |
| agcaaagagg | ttggagcaac  | aacttttttt  | tttttttttg  | cacaattgta  | attgacaggt  | 2640 |
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| ctatttgaag | aattatttta  | tacacagatt  | ctgccttggt  | tcatagtatg  | agggttgaag  | 2760 |
| acggaaaaca | atctaagggt  | ctctcatttt  | tttaattttg  | ttttgttcag  | tttggttttt  | 2820 |
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| tagctgtaat | gtttcacaga  | gtgtgctgct  | attttataaa  | cattttttata | atatattatt  | 2940 |
| ttactgctta | aattccaagt  | cctgaagtag  | atggttgaga  | tatgagttct  | tcgtactgga  | 3000 |
| aaagcccttc | cgttgcttgg  | ttctctctgg  | tagcatattc  | atgggttggtt | ttttttttct  | 3060 |
| tttttgggtt | tttggttttt  | tttttttctt  | ctgatcacat  | tcttcaaaga  | cggagtattc  | 3120 |
| tttacctcag | gtttactgga  | caaaatcaat  | aactacaaaa  | ggcaatgatt  | cacgcttttg  | 3180 |
| ttttcataat | acctcacaa   | cgtacagttt  | ctgcttgga   | gcccattcgc  | atgaggaata  | 3240 |
| cagaagcagt | gtgagcagg   | ctgactccct  | ctcaggtgga  | aggcaggcgg  | gtctcactcc  | 3300 |
| caggacctt  | tttggtcatg  | gaggccatcg  | ggctcccagt  | tagaccctgg  | tatcctcatc  | 3360 |
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| tacaaacatt | tatgcggtag  | gctcagatgt  | cgtaatttgc  | acttaggtac  | caggtgtcag  | 3480 |
| gaaacagact | aaaaagaatt  | ccaccaggct  | gtttggagat  | cctcatcttg  | gagctttttc  | 3540 |
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| ccctccctct | ggcatggaca  | ccttggtgtt  | aggatcatct  | ctgcagggtt  | cctaggtctg  | 3660 |
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| tgtctcaaac | tgcgcaggca  | agcactatgc  | aagcccaggc  | cctctgctga  | gcggtactaa  | 3780 |
| acggtcgggt | tttcaatcac  | actgaattgg  | caggataaga  | aaaataggct  | agataagtat  | 3840 |
| gggatgatag | ttgaaggagg  | gtgaagaggc  | tgcttctcta  | cagaggtgaa  | attccagatg  | 3900 |
| agtcagtctc | ttgggaagtg  | tgttttagaag | ggttcaggac  | tttgtgagtt  | agcatgaccc  | 3960 |
| taaaattcta | ggggatttct  | ggtgggacaa  | tgggtggtga  | attttgaggt  | tttgagagag  | 4020 |
| gaagtggagc | agccagcaag  | taagctagcc  | agagttttct  | caagagccag  | ctttgctcag  | 4080 |
| cacactctcc | tgggccccaa  | ggagtcccac  | ggaatgggga  | aagtgggaac  | cctggagttc  | 4140 |
| ttgggaatct | tggagcctaa  | agagaaaaccg | aggtgcaaat  | tcatttcatg  | gtgactgacc  | 4200 |

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|            |            |            |            |             |             |      |
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| taccgcactc | tatttacagt | ctgtaacttt | ccactcttcc | tgtagtcccg  | aggcccctgg  | 4320 |
| gtccttctag | cttttctctt | tcccatcctt | ggggccttgt | gtgatgatgg  | gtgtgggct   | 4380 |
| gccgatggga | aagtcggggg | ttgttaggct | tttctgcctg | ctcctgctta  | aacacaagaa  | 4440 |
| ggaatcctgg | attttgccct | ctccttagct | cttagtctct | ttggtaggag  | ttttgttcca  | 4500 |
| gaggagctct | cccccttgg  | tttgaacttg | ctctttttgt | tgttggtgtt  | ctttctcttc  | 4560 |
| tttttcttac | ctcccactaa | aggggttcca | aattatcctg | gtctttttct  | acctgtgtgt  | 4620 |
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| tgttccccca | gcctgccaaa | ttttgatcct | tcccctcttt | tggocaaatc  | ctagggggaa  | 4740 |
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| gcaggattgg | caactcttca | gacggagctg | cgcttccctg | cagtctagca  | cctctagggc  | 5160 |
| ctctccagac | tgtgccctgg | gagctctggg | actgaaaggt | taagaacata  | aggcaggatc  | 5220 |
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| ttggcttcta | agccaaaagg | attcctcttt | gtttatctct | gagacagtcc  | aaccttgaga  | 5460 |
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| tttctttttc | tttttttttt | tgttttaaaa | caagtgtgat | gccatatcaa  | gtccatgtta  | 6180 |
| ttctctcaca | gtgtactcta | taagaggtgt | gggtgtctgt | ttggtcagga  | tgttagaaag  | 6240 |
| tgttgataag | tagcatgatc | agtgtatgcg | aaaaggtttt | taggaagtat  | ggcaaaaatg  | 6300 |
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| tcagtgttaa | gtgattttaa | aaaataataa | cctgttttct | gactagttta  | aagatggatt  | 6420 |
| tgaatatggt | tttgaatgca | attaggttat | gctatttgga | caataaactc  | accttgacct  | 6480 |

&lt;210&gt; 148

&lt;211&gt; 3945

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 148

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| gatcctaccc | gagtgaggcg | gcgccatgga  | gctccgggtg  | ctgctctgct | gggcttcggt | 120 |
| ggccgcagct | ttggaagaga | ccctgctgaa  | cacaaaattg  | gaaactgctg | atctgaagtg | 180 |
| ggtgacattc | cctcagggtg | acgggcagtg  | ggaggaaactg | agcggcctgg | atgaggaaca | 240 |
| gcacagcgtg | cgcacctacg | aagtgtgtga  | agtgcagcgt  | gccccggggc | aggccactg  | 300 |
| gcttcgcaca | ggttggggtc | cacggcgggg  | cgccgtccac  | gtgtacgcca | cgctgcgctt | 360 |
| caccatgctc | gagtgccctg | ccctgcctcg  | ggctgggctg  | tcctgcaagg | agaccttcac | 420 |
| cgtcttctac | tatgagagcg | atgcggacac  | ggccacggcc  | ctcacgccag | cctggatgga | 480 |
| gaacccttac | atcaagggtg | acacgggtggc | cgcgagcat   | ctcaccggga | agcgccctgg | 540 |
| ggccgaggcc | accgggaagg | tgaatgtcaa  | gacgctgcgt  | ctgggaccgc | tcagcaaggc | 600 |
| tggcttctac | ctggccttcc | aggaccaggg  | tgcctgcatg  | gcctgctat  | ccctgcacct | 660 |
| cttctacaaa | aagtgcgccc | agctgactgt  | gaacctgact  | cgattcccgg | agactgtgcc | 720 |

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|            |             |             |             |            |             |      |
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| ctgcagctgt | gctccggggg  | tccgagcgagc | tgaggggaac  | accaagtgcc | gagcctgtgc  | 900  |
| ccagggcacc | ttcaagcccc  | tgtcaggaga  | agggtcctgc  | cagccatgcc | cagccaatag  | 960  |
| ccactctaac | accattggat  | cagccgtctg  | ccagtgccgc  | gtcgggtact | tccgggcacg  | 1020 |
| cacagacccc | cgggggtgcac | cctgcaccac  | ccctccttcg  | gctccgcgga | gcgtggtttc  | 1080 |
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| atcctcctta | gccacggggc  | ccgtcccatt  | tgagcctgtc  | aatgtcacca | ctgaccgaga  | 1380 |
| ggtacctcct | gcagtgtctg  | acatccgggt  | gacgcggtcc  | tcacccagca | gcttgagcct  | 1440 |
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| ccccttcact | tatgaagacc  | ctaatgaggc  | tgtgaggga   | tttgcaaaag | agatcgatgt  | 1920 |
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&lt;210&gt; 149

&lt;211&gt; 834

125/147

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 149

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&lt;210&gt; 150

&lt;211&gt; 4862

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 150

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 <211> 3661  
 <212> DNA  
 <213> Homo sapiens

<400> 151

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| ctggggccgg   | gactgacacc  | gcagcgcttg  | ccctgcgcca  | gggactggcg  | gctcggaggt  | 120  |
| tgcgtccacc   | ctcaagggcc  | ccagaaatca  | ctgtgttttc  | agctcagcgg  | ccctgtgaca  | 180  |
| ttccttcgtg   | ttgtcatttg  | ttgagtgacc  | aatcagatgg  | gtggagtgtg  | ttacagaaat  | 240  |
| tggcagcaag   | tatccaatgg  | gtgaagaaga  | agctaactgg  | ggacgtgggc  | agccctgacg  | 300  |
| tgatgagctc   | aaccagcaga  | gacattccat  | cccaagagag  | gtctgcgtga  | cgcgctccggg | 360  |
| aggccaccct   | cagcaagacc  | accgtacagt  | tggtggaagg  | ggtgacagct  | gcattctcct  | 420  |
| gtgcctacca   | cgtaaccaaa  | aatgaaggag  | aactactgtt  | tacaagccgc  | cctgggtgtgc | 480  |
| ctgggcatgc   | tgtgccacag  | ccatgccttt  | gccccagagc  | ggcgggggca  | cctgcggccc  | 540  |
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| ctcaacatca   | ctgtctttgc  | agcagaaatc  | cacaatcggc  | atcaggaagc  | caaagtccca  | 1860 |
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| ggtttcatct   | gtgagagtga  | tcagaccaag  | ccactttcca  | accagccaat  | tgttacaatt  | 1980 |
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&lt;210&gt; 152

&lt;211&gt; 3867

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 152

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| agcagatttg  | tatggttcca  | aagacacttt  | tgatgacgat  | tcttaacaat | aacgatacaa  | 3060 |
| atttggcctt  | aagaactgtg  | tctggcggtc  | tcaagaatct  | agaagatgtg | taaacaggta  | 3120 |
| tttttttaaa  | tcaaggaaaag | gctcatttaa  | aacaggcaaa  | gttttacaga | gaggatacat  | 3180 |
| ttaataaaaac | tgcgaggaca  | tcaaaagtgg  | aaatactgtg  | aaataacctt | tctcacaaaa  | 3240 |
| aggcaaatat  | tgaagttggt  | tatcaacttc  | gctagaaaaa  | aaaaacactt | ggcatacaaa  | 3300 |
| atattttaagt | gaaggagaag  | tctaacgctg  | aactgacaat  | gaagggaat  | tgtttatgtg  | 3360 |
| ttatgaacat  | ccaagtcttt  | cttctttttt  | aagttgtcaa  | agaagcttcc | acaaaattag  | 3420 |
| aaaggacaac  | agttctgagc  | tgtaatttcg  | ccttaaaactc | tggacactct | atatgtatgtg | 3480 |
| catttttaaa  | cttgaaatat  | ataatattca  | gccagcttaa  | accatacaa  | tgatatgtaca | 3540 |
| atacaatgta  | caattatgtc  | tcttgagcat  | caatcttggt  | actgctgatt | cttgtaaatac | 3600 |
| tttttgcttc  | tactttcatc  | ttaaaactaat | acgtgccaga  | tataactgtc | ttgtttcagt  | 3660 |
| gagagacgcc  | ctatttctat  | gtcattttta  | atgtatctat  | ttgtacaatt | ttaaagtctt  | 3720 |
| tatttttagta | tacatatataa | tatcagtatt  | ctgacatgta  | agaaaatgtt | acggcatcac  | 3780 |
| acttatattt  | tatgaacatt  | gtactgttgc  | tttaatatga  | gcttcaatat | aagaagcaat  | 3840 |
| ctttgaaata  | aaaaaagatt  | ttttttt     |             |            |             | 3867 |

&lt;210&gt; 153

&lt;211&gt; 5047

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 153

|             |             |            |             |             |             |      |
|-------------|-------------|------------|-------------|-------------|-------------|------|
| gctggatcct  | gcagtaacca  | caacagcatc | ctctccctgc  | gccagggacc  | tgccagccgg  | 60   |
| agagatgact  | gattagatca  | gattagatcc | ggagccccgc  | tctgcagaag  | ggggccccag  | 120  |
| gggcggggga  | ggaggacccc  | agctggcctg | agctgggggg  | aggggtgcct  | tggggctcgc  | 180  |
| agagttagag  | ctttccagcg  | cggggatcac | acctcagaag  | ccgccacaat  | gaaagacgga  | 240  |
| acacattttct | acacccagtg  | actggccagg | tcccagagga  | aaacaaaaaa  | tttgacttga  | 300  |
| aaatatcgac  | cttgacatg   | tccaataaaa | caggtgggaa  | acgcccggct  | accaccaaca  | 360  |
| gtgacatacc  | caaccacaac  | atggtgtccg | aggtccctcc  | agagcggccc  | agcgtccggg  | 420  |
| caactcgac   | agcccgc aaa | gccatcgctt | ttggcaagcg  | ctcacactcc  | atgaagcggg  | 480  |
| accccaatgc  | acctgtcacc  | aaggcgggct | ggctcttcaa  | acaggccagc  | tccgggggta  | 540  |
| agcagtggaa  | caagcgctgg  | ttcgtcctgg | tgatcgctg   | cctctttctac | tataaagatg  | 600  |
| agaaggaaga  | gagtatcctg  | ggcagcatcc | ccctcctgag  | cttcocgggta | gccgcagtgc  | 660  |
| agccctcaga  | caacatcagc  | cggaaacaca | cgtttaaggc  | tgagcatgcc  | gggggtccga  | 720  |
| cctactttctt | cagtgcgcag  | agccccgagg | agcaagaggc  | ctggatccag  | gccatggggg  | 780  |
| aggctgctcg  | agtacagatc  | cctccagccc | agaagtcagt  | gccccaaagt  | gtgcgggcaca | 840  |
| gccatgagaa  | gccagactcg  | gagaacgtcc | caccagcaa   | gcaccaccag  | cagccacccc  | 900  |
| acaacagcct  | ccctaagcct  | gagccagagg | ccaagactcg  | aggggagggg  | gatggccgag  | 960  |
| gctgtgagaa  | ggcagagaga  | aggcctgaga | ggccagaagt  | caagaaagag  | cctccggtga  | 1020 |
| aagccaatgg  | cctcccagct  | ggaccggagc | cagcctcaga  | gccgggcagc  | ccttaccctcg | 1080 |
| agggcccaag  | agtgccaggg  | ggtggggaac | agcctgcccc  | gccccaatgg  | tggcagtacc  | 1140 |
| actccccaag  | cgggcagggg  | agcacagctt | tcccgtctca  | ggatggagag  | actggggggac | 1200 |
| accggcggag  | tttcccacca  | cgcaccaacc | ctgacaaaat  | tgcccagcgc  | aagagctcca  | 1260 |
| tgaaccagct  | tcagcagtgg  | gtgaatctgc | cgcggggggt  | accccgcct   | gaagaccttc  | 1320 |
| ggagtccctc  | taggttctat  | cctgtgtctc | gcagggtccc  | tgagtactat  | ggccccctact | 1380 |
| cctcccagta  | ccccgatgat  | tatcagtact | acccgccagg  | agtgcggccg  | gagagcatct  | 1440 |
| gttccatgcc  | ggcctatgat  | cggatcagcc | cgccttgggc  | cctggaggag  | aagcgccatg  | 1500 |
| ccttccgcaa  | tgggggtggc  | cctgcctacc | agctgcgaga  | gtggaaggag  | cccgccagct  | 1560 |
| acgggcggca  | ggatgccacc  | gtctggatcc | caagcccctc  | ccggcagcca  | gtctattatg  | 1620 |
| atgagctgga  | tgccgcctct  | agctccctgc | gcgcctgtc   | cctgcagccc  | cgtcccaact  | 1680 |
| ctgtgccccg  | ctcaccacgc  | cagggtcctt | acagccgtgc  | ccgcatttac  | ttccctgtcc  | 1740 |
| gctcaccacg  | tgcccgtttt  | gagcggctgc | cacctcgag   | tgaggacatc  | tatgctgacc  | 1800 |
| ctgctgccta  | tgtgatgagg  | cgatccatca | gctccccc aa | ggtccctcca  | taccagaag   | 1860 |

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|            |             |            |             |             |             |      |
|------------|-------------|------------|-------------|-------------|-------------|------|
| tggtccggga | cagcctccac  | acctacaagt | taaacgagca  | agacacagat  | aagctgctgg  | 1920 |
| gaaaatttgt | tgagcagaac  | aaggtggtga | gggagcagga  | ccggctggtg  | cagcagctcc  | 1980 |
| gagctgagaa | ggagagcctg  | gaaagtgcct | tgatggggac  | ccaccaggag  | ctggagatgt  | 2040 |
| ttggaagcca | gcccgcctac  | ccagaaaagc | tgcgacacaa  | aaaggattca  | ctgcagaacc  | 2100 |
| agctcatcaa | catccgcgtg  | gagctgtctc | aggcgaccac  | ggccctgaca  | aacagcacca  | 2160 |
| tagagtatga | gcacctcgag  | tctgaggtct | ctgccctgca  | cgatgacctc  | tgggagcagc  | 2220 |
| tcaatttgga | caccagaat   | gaggtgctga | accggcaaat  | ccaaaaggag  | atctggagga  | 2280 |
| tccaggacgt | gatggagggg  | ctgaggaaga | acaaccctc   | ccggggcacg  | gacaccgcca  | 2340 |
| agcacagagg | aggacttggc  | ccctcagcca | cctacagctc  | caacagcccg  | gccagccccc  | 2400 |
| tcagctctgc | cagcctcacc  | agccccctga | gccccctttc  | actggtgtcg  | ggctctcagg  | 2460 |
| ggctccccac | caagcctggc  | tccaacgagc | ccaaggcaaa  | ctatgaacaa  | agcaagaaaag | 2520 |
| acccccacca | gacattgccc  | ctggacaccc | ccagagacat  | cagccttgtg  | cccaccaggc  | 2580 |
| aagaggtaga | ggcagagaag  | caggcagctc | tcaacaaagt  | tggcgttgtg  | ccccctcggg  | 2640 |
| caaaatcgcc | cactgatgat  | gaggtgaccc | catcagcagt  | ggtaagaagg  | aatgccagt   | 2700 |
| ggctcaccaa | tggactctcc  | tcccaggaac | gccccaaag   | tgtgtgtgtt  | cctggcgagg  | 2760 |
| ggaaggtaa  | gatgagcgtg  | gaggagcaga | ttgaccgaat  | gcggcgccac  | cagagtggct  | 2820 |
| ccatgaagga | gaagcggagg  | agcctgcagc | tcccggccag  | cccggccccc  | gacccagctc  | 2880 |
| cccggccagc | ctacaaagt   | gtgcgcccgc | accgcagcat  | ccacgaggta  | gacatctcca  | 2940 |
| acctggaggc | agccctgcgg  | gcagaggagc | ctggcgggca  | tgccctacgag | acaccccggg  | 3000 |
| aggaaattgc | ccggctctgc  | aaaatggagc | tagagcccca  | gcattatgac  | gtggacatca  | 3060 |
| ataaggagct | ctccactcca  | gacaaagtcc | tcatccctga  | acggtacatt  | gacctggagc  | 3120 |
| ctgacactcc | cctgagccct  | gaggagttag | aggagaagca  | gaagaagggt  | gagagatcca  | 3180 |
| agacactcat | tgccaaatcc  | agtatgcaga | acgtggtgcc  | catcggcgag  | ggggactctg  | 3240 |
| tggacgtgcc | ccaggactca  | gagagccagc | tgcaggagca  | ggagaagcgg  | attgaaatct  | 3300 |
| cctgcgccct | ggcgaccgag  | gcctcccgc  | ggggccgcat  | gctgtctgtg  | caatgtgcca  | 3360 |
| ccccaaagcc | tcccacctcc  | cctgcttccc | cggctcctcc  | agcaaaccct  | ctgtcgtctg  | 3420 |
| aatccccacg | gggcgcgcgac | agcagctata | ccatgcgggt  | ctgagctctg  | actgcaagcc  | 3480 |
| ctggctgagg | ccaatgctgt  | gaagctccac | agagccacat  | tctgaagccg  | tctctgccc   | 3540 |
| acctgaggtc | ctggctcccc  | accctggccc | cctgccccctg | cactcccatg  | ggaatgccgc  | 3600 |
| agggagccag | gctggggcca  | tgggctgctg | ccagaggacc  | gtggatacct  | cagtgtccac  | 3660 |
| acaccaccca | tgcccagccc  | tggagccatc | actactcaca  | ccgtgggtcc  | gggccagggc  | 3720 |
| ctgagatgac | agtggggagc  | accatcctca | ttaatgtcca  | agtcacaggg  | agcctcagcc  | 3780 |
| ttgccctggc | tgggggttgt  | gtgactccag | tggaacattc  | cctgatgggg  | gacatgccgt  | 3840 |
| ggtggagaa  | acacctgttg  | ctatcttatg | tgaggactag  | aggtgaagag  | gagatggaca  | 3900 |
| ctgcctctgg | agccagcctg  | acaccaagga | cagcacttgt  | catcatccct  | atcctcgtca  | 3960 |
| gccccaccct | gctgcctcag  | ctggaccacg | ggctttgaca  | caaaccaggt  | gctttgctta  | 4020 |
| tgggtgctcg | ctgggggtccg | gtggagactg | accaccctgc  | ttgagccaaa  | gacaaggtag  | 4080 |
| tgagagatgg | ggagaggcca  | ttggctccca | gagggaacag  | tgtgtgctgt  | ggctagagaa  | 4140 |
| cagcaggtct | gtgcagtgtc  | tgagggcagg | ttgggaagg   | tagcagagag  | agagagacag  | 4200 |
| aaagagagag | agagagagag  | agagagagag | agagagagag  | agagagatcc  | tcagagtga   | 4260 |
| aggaggggga | agcagcagga  | cacatttgca | agtcaagcag  | gaaggaggga  | gatggaaaag  | 4320 |
| ggatatcaga | ttgggtttccc | ccggtggagc | cttaggttag  | tgcccagtg   | agtgccagac  | 4380 |
| tgtctcctct | gctcctccca  | cctcatccct | aggaggaccc  | accagtggag  | cacatgcagc  | 4440 |
| ctcagtggag | atgcttggtg  | tggggatctg | ggtgaagggg  | ggtgagtagc  | gactgcctgg  | 4500 |
| gagatggctg | ttagtaggtc  | tgcgcctggt | gtctgcctcg  | ccatcctggg  | gtaaggggca  | 4560 |
| gagagaagga | cttgtcttat  | gtagggtgtg | gtcagccttg  | gggccttacc  | taccagttc   | 4620 |
| catgatattt | cttgccctgt  | tccccctgga | atgtgcagtg  | ggccagctga  | gagtagccct  | 4680 |
| tgaggagggg | ggatgaggcc  | ttaatctggg | aggcctatcc  | ccctatccca  | ggcatccag   | 4740 |
| acgaggactg | gctgaggcta  | ggcgctctca | tgatccacct  | gccccgggag  | ggcagcgggg  | 4800 |
| aagacagaga | aaagcaaaaca | cattcctcct | cagctccacc  | cacctggaga  | cgaatgtagc  | 4860 |
| cagagaggag | gaaggaggga  | aactgaaaac | accgtggccc  | ctcgcccttc  | tctctgctag  | 4920 |
| agttgccgct | cagaggcttc  | agcctgactt | ccagcggctc  | caagaacacc  | tactaattcc  | 4980 |
| tctccactcc | ttcatggctg  | ggacagttac | tggttcatat  | gcaagtaaag  | atgacaattt  | 5040 |
| actcaac    |             |            |             |             |             | 5047 |

&lt;210&gt; 154

&lt;211&gt; 3372

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 154

|             |             |             |            |             |            |      |
|-------------|-------------|-------------|------------|-------------|------------|------|
| tacaaccagg  | ctcaactggt  | gcatggtagc  | agatttgcaa | acatgagtgc  | tgaggggtac | 60   |
| cagtacagag  | cgctgtatga  | ttataaaaaag | gaaagagaag | aagatattga  | cttgcacttg | 120  |
| ggtgacatat  | tgactgtgaa  | taaaggggtcc | ttagtagctc | ttggattcag  | tgatggacag | 180  |
| gaagccaggc  | ctgaagaaat  | tggctggtta  | aatggctata | atgaaaccac  | aggggaaaag | 240  |
| ggggactttc  | cgggaaactta | cgtagaatat  | attggaagga | aaaaaatctc  | gcctcccaca | 300  |
| ccaaagcccc  | ggccacctcg  | gcctcttccct | gttgaccag  | gttcttcgaa  | aactgaagca | 360  |
| gatgttgaac  | aacaagcttt  | gactctcccc  | gatcttgag  | agcagtttgc  | ccctcctgac | 420  |
| attgccccgc  | ctcttcttat  | caagctcgtg  | gaagccattg | aaaagaaaag  | tctggaatgt | 480  |
| tcaactctat  | acagaacaca  | gagctccagc  | aacctggcag | aattacgaca  | gcttcttgat | 540  |
| tgtgatacac  | cctccgtgga  | cttggaaatg  | atcgatgtgc | acgttttggc  | tgacgctttc | 600  |
| aaacgctatc  | tcctggactt  | accaaactcct | gtcattccag | cagccgttta  | cagtgaatg  | 660  |
| atctctttag  | ctccagaagt  | acaaagctcc  | gaagaatata | ttcagctatt  | gaagaagctt | 720  |
| attaggtcgc  | ctagcatacc  | tcatacagtat | tggcttacgc | ttcagtat    | gttaaaacat | 780  |
| ttcttcaagc  | tctctcaaac  | ctccagcaaa  | aatctgttga | atgcaagagt  | actctctgaa | 840  |
| atcttcagcc  | ctatgctttt  | cagatttctca | gcagccagct | ctgataatac  | tgaaaacctc | 900  |
| ataaaagtta  | tagaaatttt  | aatctcaact  | gaatggaatg | aacgacagcc  | tgaccagca  | 960  |
| ctgcctccta  | aaccaccaa   | acctactact  | gtagccaaca | acggtatgaa  | taacaatatg | 1020 |
| tccttaca    | atgctgaatg  | gtactgggga  | gatatctcga | gggaagaagt  | gaatgaaaaa | 1080 |
| cttcgagata  | cagcagacgg  | gacctttttg  | gtacgagatg | cgtctactaa  | aatgcatggt | 1140 |
| gattatactc  | ttacactaag  | gaaaggggga  | aataacaaat | taatcaaaat  | atctcatcga | 1200 |
| gatgggaaat  | atggcttctc  | tgaccattta  | accttcagtt | ctgtgggtga  | attaataaac | 1260 |
| cactaccgga  | atgaatctct  | agctcagtat  | aatcccaaat | tggatgtgaa  | attactttat | 1320 |
| ccagtatcca  | aataccaaca  | ggatcaagtt  | gtcaaagaag | ataatattga  | agctgtaggg | 1380 |
| aaaaaattac  | atgaatataa  | cactcagttt  | caagaaaaaa | gtcgagaata  | tgatagatta | 1440 |
| tatgaagaat  | atccccgcac  | atcccaggaa  | atccaaatga | aaaggacagc  | tattgaagca | 1500 |
| tttaattgaaa | ccataaaaat  | atgtgaagaa  | cagtgccaga | cccaagagcg  | gtacagcaaa | 1560 |
| gaatacatag  | aaaagtttaa  | acgtgaaggc  | aatgagaaag | aaatacaaaag | gattatgcat | 1620 |
| aattatgata  | agttgaagtc  | tcgaatcagt  | gaaattattg | acagtagaag  | aagattggaa | 1680 |
| gaagacttga  | agaagcaggc  | agctgagtat  | cgagaaattg | acaaacgtat  | gaacagcatt | 1740 |
| aaaccagacc  | ttatccagct  | gagaaagacg  | agagaccaat | acttgatgtg  | gttgactcaa | 1800 |
| aaaggtgttc  | ggcaaaaagaa | gttgaacgag  | tggttgggca | atgaaaacac  | tgaagacca  | 1860 |
| tattcactgg  | tggaagatga  | tgaagatttg  | ccccatcatg | atgagaagac  | atggaatggt | 1920 |
| ggaagcagca  | accgaaacaa  | agctgaaaac  | ctgttgcgag | ggaagcgaga  | tggaactttt | 1980 |
| cttgctcggg  | agagcagtaa  | acagggtcgc  | tatgctgtct | ctgtagtggg  | ggacggcgaa | 2040 |
| gtaaagcatt  | gtgtcataaa  | caaaacagca  | actggctatg | gctttgcccga | gccctataac | 2100 |
| ttgtacagct  | ctctgaaaga  | actggtgcta  | cattaccaac | acacctccct  | tgtgcagcac | 2160 |
| aacgactccc  | tcaatgtcac  | actagcctac  | ccagtatatg | cacagcagag  | gcgatgaagc | 2220 |
| gcttactctt  | tgatccttct  | cctgaagttc  | agccaccctg | aggcctctgg  | aaagcaaaag | 2280 |
| gctcctctcc  | agtctgatct  | gtgaattgag  | ctgcagaaac | gaagccatct  | ttctttggat | 2340 |
| gggactagag  | ctttctttca  | caaaaaagaa  | gtaggggaag | acatgcagcc  | taaggctgta | 2400 |
| tgatgaccac  | acgttcctaa  | gctggagtgc  | ttatcccttc | tttttctttt  | tttctttggg | 2460 |
| ttaattttaa  | gccacaacca  | catacaacac  | aaagagaaaa | agaaatgcaa  | aaatctctgc | 2520 |
| gtgcagggac  | aaagaggcct  | ttaacatggt  | tgcttgtaa  | tgctttctga  | agctttacca | 2580 |
| gctgaaagtt  | gggactctgg  | agagcggagg  | agagagaggc | agaagaacc   | tggcctgaga | 2640 |
| aggtttgggtc | cagcctgggt  | tagcctggat  | gttgctgtgc | acggtggacc  | cagacacatc | 2700 |
| gcactgtgga  | ttatttcatt  | ttgtaacaaa  | tgaacgatat | gtagcagaaa  | ggcacgtcca | 2760 |
| ctcacaaggg  | acgctttggg  | agaatgtcag  | ttcatgtatg | ttcagaagaa  | attctgtcat | 2820 |
| agaaagtgcc  | agaaagtgtt  | taacttgtca  | aaaaacaaaa | accagcaac   | agaaaaatgg | 2880 |
| agtttgga    | acaggactta  | aatgacatt   | cagtatataa | aatatgtaca  | taatatggga | 2940 |
| tgactaacta  | tcaaatagat  | ggattttgat  | caataccaaa | tagcttctgt  | tttggtttgc | 3000 |
| tgaaggctaa  | attcacagcg  | ctatgcaatt  | cttaattttc | attaagtgtg  | tatttcagtt | 3060 |
| ttaaagtgtac | cttcagaata  | agcttcccca  | ccccagtttt | tgttgcttga  | aaatattggt | 3120 |
| gtcccggatt  | tttggttaata | ttcatttttg  | ttatcctttt | ttaaaaaata  | atgtacagga | 3180 |
| tgccagtaaa  | aaaaaaaaatg | gcttcagaat  | taaaactatg | aaatatttta  | cagtttttct | 3240 |

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|            |            |            |            |            |              |      |
|------------|------------|------------|------------|------------|--------------|------|
| tgtacagagt | acttgctggt | agcccaaggt | taaaaagttc | ataacagatt | ttttttggac   | 3300 |
| tgttttgttg | ggcagtgcc  | gataagcttc | aaagctgctt | tattcaataa | aaaaaaaaaacc | 3360 |
| cgaattcact | gg         |            |            |            |              | 3372 |

&lt;210&gt; 155

&lt;211&gt; 4139

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 155

|             |             |             |            |            |            |      |
|-------------|-------------|-------------|------------|------------|------------|------|
| ccgctccacc  | tctcaagcag  | ccagcgccctg | cctgaatctg | ttctgcccc  | tccccaccca | 60   |
| tttcaccacc  | accatgacac  | cgggcaccca  | gtctcctttc | ttcctgctgc | tgtcctcac  | 120  |
| agtgcttaca  | gttggttacag | gttctggtca  | tgcaagctct | acccaggtg  | gagaaaagga | 180  |
| gacttcggct  | acccagagaa  | gttcagtgcc  | cagctctact | gagaagaatg | ctgtgagtat | 240  |
| gaccagcagc  | gtactctcca  | gccacagccc  | cggttcaggc | tcctccacca | ctcagggaca | 300  |
| ggatgtcact  | ctggccccgg  | ccacggaacc  | agcttcaggt | tcagctgcca | cctggggaca | 360  |
| ggatgtcacc  | tccgtcccag  | tcaccaggcc  | agccctgggc | tccaccaccc | cgccagccca | 420  |
| cgatgtcacc  | tcagccccgg  | acaacaagcc  | agccccgggc | tccaccgccc | ccccagccca | 480  |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 540  |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 600  |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 660  |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 720  |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 780  |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 840  |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 900  |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 960  |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1020 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1080 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1140 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1200 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1260 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1320 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1380 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1440 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1500 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1560 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1620 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1680 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1740 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1800 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1860 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1920 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 1980 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 2040 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 2100 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 2160 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 2220 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 2280 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 2340 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 2400 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 2460 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 2520 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 2580 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 2640 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 2700 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 2760 |
| cgggtgtcacc | tcggccccgg  | acaccaggcc  | ggccccgggc | tccaccgccc | ccccagccca | 2820 |

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|             |             |            |            |            |             |      |
|-------------|-------------|------------|------------|------------|-------------|------|
| cgggtgtcacc | tcggcccccg  | acaccaggcc | ggccccgggc | tccaccgccc | ccccagccca  | 2880 |
| tggtgtcacc  | tcggcccccg  | acaacaggcc | cgccttgggc | tccaccgccc | ctccagtcca  | 2940 |
| caatgtcacc  | tcggccctcag | gctctgcac  | aggctcagct | tctactctgg | tgcacaacgg  | 3000 |
| cacctctgcc  | agggctacca  | caaccccagc | cagcaagagc | actccattct | caattcccag  | 3060 |
| ccaccactct  | gatactccta  | ccacccttgc | cagccatagc | accaagactg | atgccagtag  | 3120 |
| cactcaccat  | agctcggtag  | ctcctctcac | ctcctccaat | cacagcactt | ctccccagtt  | 3180 |
| gtctactggg  | gtctctttct  | ttttcctgtc | ttttcacatt | tcaaacctcc | agtttaattc  | 3240 |
| ctctctggaa  | gatcccagca  | ccgactacta | ccaagagctg | cagagagaca | tttctgaaat  | 3300 |
| gtttttgcag  | atttataaac  | aaggggggtt | tctgggcctc | tccaatatta | agttcaggcc  | 3360 |
| aggatctgtg  | gtggtacaat  | tgactctggc | cttccgagaa | ggtaccatca | atgtccacga  | 3420 |
| cgtggagaca  | cagttcaatc  | agtataaaac | ggaagcagcc | tctcgatata | acctgacgat  | 3480 |
| ctcagacgtc  | agcgtgagtg  | atgtgccatt | tcctttctct | gccagtcctg | gggctggggg  | 3540 |
| gccaggctgg  | ggcatcgcgc  | tgctgggtgt | ggtctgtgtt | ctgggtgcgc | tggccattgt  | 3600 |
| ctatctcatt  | gccttggctg  | tctgtcagtg | ccgccgaaag | aactacgggc | agctggacat  | 3660 |
| ctttccagcc  | cgggatacct  | accatcctat | gagcgagtag | cccacctacc | acacccatgg  | 3720 |
| gcgctatgtg  | ccccctagca  | gtaccgatcg | tagcccctat | gagaagggtt | ctgcaggtaa  | 3780 |
| cgggtggcagc | agcctctctt  | acacaaaacc | agcagtggca | gccgcttctg | ccaacttgta  | 3840 |
| gggcacgtcg  | ccgctgagct  | gagtggccag | ccagtgccat | tccactccac | tcagggttctt | 3900 |
| caggccagag  | cccctgcacc  | ctgtttgggc | tggtgagctg | ggagttcagg | tgggctgctc  | 3960 |
| acagcctcct  | tcagaggccc  | caccaatttc | tcggacactt | ctcagtgtgt | ggaagctcat  | 4020 |
| gtgggccccct | gaggtcatg   | cctgggaagt | gttgtggggg | ctcccaggag | gactggccca  | 4080 |
| gagagccctg  | agatagcggg  | gatcctgaac | tggactgaat | aaaacgtggt | ctcccactg   | 4139 |

&lt;210&gt; 156

&lt;211&gt; 4879

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 156

|            |             |            |            |            |             |      |
|------------|-------------|------------|------------|------------|-------------|------|
| accaattcgc | cagcgggttca | ggtgggtctt | gcctcgatgt | cctagcctag | gggcccccg   | 60   |
| gccggacttg | gctgggctcc  | cttcaaccct | tgccgagtag | tgagggcgaa | cgacgctctg  | 120  |
| caggtgctgg | gcttgctttt  | cagcctggcc | cggggctccg | aggtgggcaa | ctctcaggca  | 180  |
| gtgtgtcctg | ggactctgaa  | tggcctgagt | gtgaccggcg | atgctgagaa | ccaataccag  | 240  |
| acactgtaca | agctctacga  | gaggtgtgag | gtggtgatgg | ggaaccttga | gattgtgctc  | 300  |
| acgggacaca | atgccgacct  | ctccttccct | cagtggattc | gagaagtga  | aggctatgtc  | 360  |
| ctcgtggcca | tgaatgaatt  | ctctactcta | ccattgccca | acctccgcgt | ggtgcgaggg  | 420  |
| acccaggtct | acgatgggaa  | gtttgccatc | ttcgtcatgt | tgaactataa | caccaactcc  | 480  |
| agccacgctc | tgcgcagctc  | ccgcttgact | cagctcaccg | agattctgtc | aggggggtgt  | 540  |
| tatatgtaga | agaacgataa  | gctttgtcac | atggacacaa | ttgactggag | ggacatcggt  | 600  |
| agggaccgag | atgctgagat  | agtgggtga  | gacaatggca | gaagctgtcc | cccctgtcat  | 660  |
| gaggtttgca | aggggcgatg  | ctggggctct | ggatcagaag | actgccagac | attgaccaag  | 720  |
| accatctgtg | ctcctcagtg  | taatggctac | tgctttgggc | ccaaccccaa | ccagtgtctc  | 780  |
| catgatgagt | gtgccggggg  | ctgctcaggc | cctcaggaca | cagactgctt | tgcctgccgg  | 840  |
| cacttcaatg | acagtggagc  | ctgtgtacct | cgctgtccac | agcctcttgt | ctacaacaag  | 900  |
| ctaactttcc | agctggaacc  | caatccccac | accaagtatc | agtatggagg | agtttgtgta  | 960  |
| gccagctgtc | cccataactt  | tgtggtggat | caaacatcct | gtgtcagggc | ctgtcctcct  | 1020 |
| gacaagatgg | aagttagataa | aaatgggctc | aagatgtgtg | agccttgttg | gggactatgt  | 1080 |
| cccaaagcct | gtgagggaac  | aggctctggg | agccgcttcc | agactgtgga | ctogagcaac  | 1140 |
| attgatggat | ttgtgaactg  | caccaagatc | ctgggcaacc | tggactttct | gatcaccggc  | 1200 |
| ctcaatggag | acccctggca  | caagatccct | gccctggacc | cagagaagct | caatgtcttc  | 1260 |
| cggacagtag | gggagatcac  | aggttacctg | aacatccagt | cctggccgcc | ccacatgcac  | 1320 |
| aacttcagtg | ttttttccaa  | tttgacaacc | attggaggca | gaagcctcta | caaccggggc  | 1380 |
| ttctcattgt | tgatcatgaa  | gaacttgaat | gtcacatctc | tgggcttccg | atccctgaag  | 1440 |
| gaaattagtg | ctgggcgtat  | ctatataagt | gccaataggc | agctctgcta | ccaccactct  | 1500 |
| ttgaactgga | ccaaggtgct  | tcgggggcct | acggaagagc | gactagacat | caagcataat  | 1560 |
| cggccgcgca | gagactgcgt  | ggcagagggc | aaagtgtgtg | acccactgtg | ctcctctggg  | 1620 |
| ggatgctggg | gcccaggccc  | tggtcagtg  | ttgtcctgtc | gaaattatag | ccgaggagggt | 1680 |

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|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| gtctgtgtga  | cccactgcaa  | ctttctgaat  | ggggagcctc  | gagaattttgc | ccatgaggcc  | 1740 |
| gaatgcttct  | cctgccaccc  | ggaatgccaa  | cccatggagg  | gcactgccac  | atgcaatggc  | 1800 |
| tcgggctctg  | atacttgtgc  | tcaatgtgcc  | cattttcgag  | atgggcccc   | ctgtgtgagc  | 1860 |
| agctgcccc   | atggagtcct  | aggtgccaa   | ggcccaatct  | acaagtacc   | agatgttcag  | 1920 |
| aatgaatgtc  | ggccctgcca  | tgagaactgc  | acccaggggt  | gtaaaggacc  | agagcttcaa  | 1980 |
| gactgtttag  | gacaaacact  | ggtgctgac   | ggcaaaaccc  | atctgacaat  | ggctttgaca  | 2040 |
| gtgatagcag  | gattggtagt  | gattttcatg  | atgctgggcg  | gcacttttct  | ctactggcgt  | 2100 |
| gggcgcggga  | ttcagaataa  | aagggtatg   | aggcgatact  | tggaacgggg  | tgagagcata  | 2160 |
| gagcctctgg  | acccagtgga  | gaaggctaac  | aaagtcttgg  | ccagaatctt  | caaagagaca  | 2220 |
| gagctaagga  | agcttaaagt  | gcttggtctg  | ggtgtctttg  | gaactgtgca  | caaaggagtg  | 2280 |
| tgatccctg   | agggggaatc  | aatcaagatt  | ccagctctgca | ttaaagtcac  | tgaggacaag  | 2340 |
| agtggacggc  | agagttttca  | agctgtgaca  | gatcatatgc  | tggccattgg  | cagcctggac  | 2400 |
| catgccaca   | ttgtaaggct  | gctgggacta  | tgcccagggt  | catctctgca  | gcttgtcact  | 2460 |
| caatatttgc  | ctctgggttc  | tctgctggat  | catgtgagac  | aacaccgggg  | ggcactgggg  | 2520 |
| ccacagctgc  | tgctcaactg  | gggagtacaa  | attgccaagg  | gaatgtacta  | ccttgaggaa  | 2580 |
| catggtatgg  | tgcatagaaa  | cctggctgcc  | cgaaacgtgc  | tactcaagtc  | acccagtcag  | 2640 |
| gttcagggtg  | cagatttttg  | tgtggctgac  | ctgctgcctc  | ctgatgataa  | gcagctgcta  | 2700 |
| tacagtgagg  | ccaagactcc  | aattaagtgg  | atggcccttg  | agagtatcca  | ctttgggaaa  | 2760 |
| tacacacacc  | agagtgatgt  | ctggagctat  | ggtgtgacag  | tttgggagtt  | gatgaccttc  | 2820 |
| ggggcagagc  | cctatgcagg  | gctacgattg  | gctgaagtac  | cagacctgct  | agagaagggg  | 2880 |
| gagcggttgg  | cacagcccca  | gatctgcaca  | gatgatgtct  | acatggtgat  | ggtcaagtgt  | 2940 |
| tggtatgattg | atgagaacat  | tcgcccaccc  | tttaaagaac  | tagccaatga  | gttcaccagg  | 3000 |
| atggcccag   | acccaccacg  | gtatctggtc  | ataaagagag  | agagtggggc  | tggaatagcc  | 3060 |
| cctgggccag  | agccccatgg  | tctgacaaac  | aagaagctag  | aggaagtaga  | gctggagcca  | 3120 |
| gaactagacc  | tagacctaga  | cttggaagca  | gaggaggaca  | acctggcaac  | caccacactg  | 3180 |
| ggctccgccc  | tcagcctacc  | agttggaaca  | cttaatcggc  | cacgtgggag  | ccagagcctt  | 3240 |
| ttaagtccat  | catctggata  | catgcccctg  | aaccagggtg  | atcttgggga  | gtcttggccag | 3300 |
| gagtctgcag  | tttctgggag  | cagtgaacgg  | tgcccccgct  | cagtctctct  | acacccaatg  | 3360 |
| ccacggggat  | gcctggcacc  | agagtcatca  | gaggggcatg  | taacaggctc  | tgaggctgag  | 3420 |
| ctccaggaga  | aagtgtcaat  | gtgtagaagc  | cggagcagga  | gccggagccc  | acggccacgc  | 3480 |
| ggagatagcg  | cctaccatcc  | ccagcgccac  | agtctgctga  | ctcctgttac  | cccactctcc  | 3540 |
| ccacccgggt  | tagaggaaga  | ggatgtcaac  | ggttatgtca  | tgccagatac  | acacctcaaa  | 3600 |
| ggtactccct  | cctcccggga  | aggcaccctt  | tcttcagttg  | gtcttagttc  | tgtcctgggt  | 3660 |
| actgaagaag  | aagatgaaga  | tgaggagtat  | gaatacatga  | accggaggag  | aaggcacagt  | 3720 |
| ccacctcatc  | cccctaggcc  | aagttccctt  | gaggagctgg  | gttatgagta  | catggatgtg  | 3780 |
| gggtcagacc  | tcagtgcctc  | tctgggcagc  | acacagagtt  | gcccactcca  | ccctgtaccc  | 3840 |
| atcatgcccc  | ctgcaggcac  | aactccagat  | gaagactatg  | aatatatgaa  | tcggcaacga  | 3900 |
| gatggagtg   | gtcctggggg  | tgattatgca  | gccatggggg  | cctgccagc   | atctgagcaa  | 3960 |
| gggtatgaag  | agatgagagc  | ttttcagggg  | cctggacatc  | aggcccccca  | tgtccattat  | 4020 |
| gcccgcctaa  | aaactctacg  | tagcttagag  | gctacagact  | ctgcctttga  | taacctgat   | 4080 |
| tactggcata  | gcaggctttt  | ccccaaggct  | aatgcccaga  | gaacgtaact  | cctgctccct  | 4140 |
| gtggcactca  | gggagcattt  | aatggcagct  | agtgccttta  | gagggtaccg  | tcttctccct  | 4200 |
| attccctctc  | tctcccaggt  | cccagccctt  | tttcccagct  | cccagacaat  | tccattcaat  | 4260 |
| ctttggaggc  | ttttaaacat  | tttgacacaa  | aattcttatg  | gtatgtagcc  | agctgtgcac  | 4320 |
| tttcttctct  | ttcccaaccc  | caggaaagggt | tttccttatt  | ttgtgtgctt  | tcccagtooc  | 4380 |
| attcctcagc  | ttcttcacag  | gcactcctgg  | agatatgaag  | gattactctc  | catatccctt  | 4440 |
| cctctcaggc  | tcttgactac  | ttggaactag  | gctccttatgt | gtgcctttgt  | ttcccatcag  | 4500 |
| actgtcaaga  | agaggaaaag  | gaggaaaacct | agcagaggaa  | agtgtaatth  | tggtttatga  | 4560 |
| ctcttaaccc  | cctagaaaaga | cagaagctta  | aaatctgtga  | agaaagagggt | taggagtaga  | 4620 |
| tattgattac  | tatcataatt  | cagcaacttaa | ctatgagcca  | ggcatcatac  | taaacttcac  | 4680 |
| ctacattatc  | tacttagtgc  | ctttatcatc  | cttaaaacaa  | ttctgtgaca  | tacatattat  | 4740 |
| ctcatttttac | acaaagggaa  | gtcgggcatg  | gtggctcatg  | cctgtaatct  | cagcactttg  | 4800 |
| ggaggctgag  | gcagaaggat  | tacctgaggg  | aaggagtthg  | agaccagctt  | agccaacata  | 4860 |
| gtaagacccc  | catctctttt  |             |             |             |             | 4879 |

&lt;210&gt; 157

&lt;211&gt; 1611

135/147

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 157

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gaattctgaa tataggacac gaatttatga tccttagcaa tgtgaagtta gagaaggggt 60
tttattgtga aattgacaca ggttgtttta tatcttataa atgaagtctc ctcatTTTTcc 120
tgtggtcaga agagaggggg caagcagaaa agcagaggaa caaatttgga ggctaaaata 180
acattctaca taaggaaacta tactacagta gaattaattg atagcaggga ttaagagatg 240
taaatgaatt tgagatacat attctagagg tagaatgtgc aatactTTTT gtatgtccat 300
atacagaaat tggttgcatt ttctttaa ataaagattt tttaaaagtc agtgagctgt 360
tatgttttct tccctctgac ttcaattcct tgattctttc aattttttta atataaattt 420
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gtgggctggg cacactgagt ttccagtttcc tttctctgag tctttgaagc ttcaaggctg 540
ctgaataatt tccttctccc attttgtgcc tgcctagcta tccagacaga gcagctaccc 600
tcagctctag ctgatactac agacagtaca acaggtaa atgtcttctgc ttttcatttt 660
tcctagctag cattagtctc tctctgtctc tctcagggtga cagtgtccat tgcaatctca 720
gtttttgttt taatttaaaa aacaataatt tatagtaaaa aattagctaa tgattttttt 780
gctttctgtt catcctttgt tttgtcattt tttgtattat gtagagtata taagaggcat 840
aaatgcaaat tttataacta catattatct gttttttaat atttaattgga aaatatatat 900
gatttgccac tagatcaaga agtatggcag tgacaactcg tttgacatgg ttgcacgaaa 960
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ttggacttgc tcaaaattgt actatctcta ttcaggatta tgaagttttt cgatgcgaag 1380
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ctgaaacctg gatacagatt gtttgctaag agacaacat ggtcaataaa atgtatatatt 1560
atgataagaa cccttaacgt aagatttatc ctcttagcac attttaagta c 1611

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&lt;210&gt; 158

&lt;211&gt; 155

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 158

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gaattcactg atattcatctc attcattcag ccaattattc gacaacttct aatctacatt 60
attctttgat tatttcccca gattcactgg atgaaagaaa gataaaagggt gtcattgagt 120
aagtcaatgt ttttaagatt ctattactct cttca 155

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&lt;210&gt; 159

&lt;211&gt; 312

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 159

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tttgcgacct aacctcagtc aattgttaaa aacggtcatt tctaaacagg ctcaggaaga 60
gcttactgtc tgccttgaga acttatgaac catatggatc cctggttcaa caaatacgaa 120
ttctctcctt gggctcaatt ggagctccca agtccagctt tttcaactca gtgagggtctg 180
ttttccaagg gcatgtaacg catcaggctt tgggtgggcac taatacaact gggatatctg 240
agaaggtaag cacatttgag gccacctagc ctttgcttct ctgttcaaat caattatatt 300
tcaaaagctt tt 312

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<210> 160  
 <211> 447  
 <212> DNA  
 <213> Homo sapiens

<400> 160  
 ggccacctag cctttgcttc tctgttcaaa tcaattatat ttcaaaagcc ttttgcagat 60  
 caacttttatt acatatagac ttcatctcaa ttataataa aaaatgaatc tttaaaattg 120  
 cttttctccc ctctacagta taggacatac tctattagag acgggaaaga tggcaaatac 180  
 ctgccgttta ttctgtgtga ctcaactggg ctgagtgaga aagaaggcgg cctgtgcagg 240  
 gatgacatat tctatatctt gaacggtaac attcgtgata gataccagg taaattttgac 300  
 taatgagaaa ttataactga tttttaaaat gcttattttt gtacaaatgt atcagcgttt 360  
 atcttcttaa attatacttg ctcaagatcc tttgtctctt ttagattttt tttttcaaaa 420  
 agaataaaaa catctcgagg gctcttc 447

<210> 161  
 <211> 341  
 <212> DNA  
 <213> Homo sapiens

<400> 161  
 ttgtgctcat aaatatttgt tgaattaata tcttgcttta tgtctacctt acagtttaat 60  
 cccatggaat caatcaaatt aaatcatcat gactacattg attccccatc gctgaaggac 120  
 agaattcatt gtgtggcatt tgtatttgat gccagctcta ttcaatactt ctctctcag 180  
 atgatagtaa agatcaaaaag aattcaaagg gagttggtga acgctggtga gtctcattcc 240  
 actttgctaa gggtaatacc actaagggtg attgactaga ctgtatttta gaatgctttt 300  
 tggacaggat aaagaactta agtcattgca tatttcaatc t 341

<210> 162  
 <211> 288  
 <212> DNA  
 <213> Homo sapiens

<400> 162  
 gatctttcca aatctgaaat tggtccatag gttgcctatt acataattga tagttaaata 60  
 acttgaaaaa actgatgctc tctaaaatga tttaaaaaat tctgtttggc ataggtgtgg 120  
 tacatgtggc ttgtctcact catgtggata gcatggattt gattacaaaa ggtgacctta 180  
 tagaaataga gagatgtgag cctgtgaggt ccaaggtaat gaatgatgcc cttcgtaaac 240  
 acattttctg gggatatgta ctacaatcac atactagtgt gtataaaa 288

<210> 163  
 <211> 372  
 <212> DNA  
 <213> Homo sapiens

<400> 163  
 tttttttcca atggaaatta ttgcaagttc ctacatcttg atattgcttt cataatttat 60  
 actaacataa aataatattt ttcaactgtt tgcaatgtct ttttaatttc tgtattgcag 120  
 ctagaggaag tccaaagaaa acttggaatt gctctttctg acatctcggg ggtagcaat 180  
 tattcctctg agtgggagct ggaccctgta aaggatgttc taattctttc tgctctgaga 240  
 cgaatgctat gggctgcaga tgacttctta gaggatttgc cttttgagca aataggtaga 300  
 tggtttggtg gtgtggaagc ttggaagcgg tcaggtagtt ggctactttc tgcttggatc 360  
 tattaataac tg 372

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<210> 164  
 <211> 483  
 <212> DNA  
 <213> Homo sapiens

<400> 164  
 cctctggttg cctttcctga gataatccac taagaatatt ttgtgtttct tttctcaggg 60  
 aatctaaggg aggaaattat caactgtgca caaggaaaaa aatagatatg tgaaagggttc 120  
 acgtaaattt cctcacatca cagaagatta aaattcagaa aggagaaaac acagacccaaa 180  
 gagaagtatc taagacccaa gggatgtgtt ttattaatgt ctaggatgaa gaaatgcata 240  
 gaacattgta gtacttgtaa ataactagaa ataacatgat ttagtcataa ttgtgaaaaa 300  
 taataataat ttttcttgga tttatgttct gtatctgtga aaaaataaat ttcttataaa 360  
 actcgggtct aacttgagag tgtgtgtgat tttggaaaaa ttatgatttg tcagcatctt 420  
 ctgatattca ctgctttcat cttaattttg ccttctgatt ttatttctaa agtatgtgat 480  
 ttt 483

<210> 165  
 <211> 25  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: Primer

<400> 165  
 gctctcttat ttgtaccggt ttttg 25

<210> 166  
 <211> 24  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: Primer

<400> 166  
 aagctagtga ctgtcaccga tcag 24

<210> 167  
 <211> 16  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: Probe

<400> 167  
 tcatgtttcc aatctc 16

<210> 168  
 <211> 30  
 <212> DNA  
 <213> Artificial Sequence

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<220>  
<223> Description of Artificial Sequence: Primer  
  
<400> 168  
cctgatataa atgcaatatt aatgccttta 30  
  
<210> 169  
<211> 21  
<212> DNA  
<213> Artificial Sequence  
  
<220>  
<223> Description of Artificial Sequence: Primer  
  
<400> 169  
aagaaccggg agagcaaaca t 21  
  
<210> 170  
<211> 20  
<212> DNA  
<213> Artificial Sequence  
  
<220>  
<223> Description of Artificial Sequence: Probe  
  
<400> 170  
atctatgcc aagatcactt 20  
  
<210> 171  
<211> 17  
<212> DNA  
<213> Artificial Sequence  
  
<220>  
<223> Description of Artificial Sequence: Primer  
  
<400> 171  
ggagcaccgc ctgtgaa 17  
  
<210> 172  
<211> 20  
<212> DNA  
<213> Artificial Sequence  
  
<220>  
<223> Description of Artificial Sequence: Primer  
  
<400> 172  
tgtgcgttgc ctgaatgaac 20  
  
<210> 173  
<211> 16

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<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Probe

<400> 173  
accaacctga agacac 16

<210> 174  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 174  
tctcgactga atggactttg ca 22

<210> 175  
<211> 18  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 175  
ttgtgtaccc cgcaccaa 18

<210> 176  
<211> 17  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Probe

<400> 176  
cacacctcta tcccggc 17

<210> 177  
<211> 20  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 177  
gctgcatgtg gatcctgaga 20

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<210> 178  
 <211> 25  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: Primer

<400> 178  
 tgagtagcca gaataatcac catca 25

<210> 179  
 <211> 18  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: Probe

<400> 179  
 cttcaagctc ctgggtaa 18

<210> 180  
 <211> 136  
 <212> DNA  
 <213> Homo sapiens

<400> 180  
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 cagtgccacc catgcagctg ctccccaggc caccocgctg atggagcccc accttgtctg 120  
 ctaaataaac atgtgc 136

<210> 181  
 <211> 1066  
 <212> PRT  
 <213> Homo sapiens

<400> 181  
 Met Pro Val Phe His Thr Arg Thr Ile Glu Ser Ile Leu Glu Pro Val  
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 Ala Gln Gln Ile Ser His Leu Val Ile Met His Glu Glu Gly Glu Val  
 20 25 30  
 Asp Gly Lys Ala Ile Pro Asp Leu Thr Ala Pro Val Ala Ala Val Gln  
 35 40 45  
 Ala Ala Val Ser Asn Leu Val Arg Val Gly Lys Glu Thr Val Gln Thr  
 50 55 60  
 Thr Glu Asp Gln Ile Leu Lys Arg Asp Met Pro Pro Ala Phe Ile Lys  
 65 70 75 80  
 Val Glu Asn Ala Cys Thr Lys Leu Val Gln Ala Ala Gln Met Leu Gln  
 85 90 95

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Ser Asp Pro Tyr Ser Val Pro Ala Arg Asp Tyr Leu Ile Asp Gly Ser  
 100 105 110  
 Arg Gly Ile Leu Ser Gly Thr Ser Asp Leu Leu Leu Thr Phe Asp Glu  
 115 120 125  
 Ala Glu Val Arg Lys Ile Ile Arg Val Cys Lys Gly Ile Leu Glu Tyr  
 130 135 140  
 Leu Thr Val Ala Glu Val Val Glu Thr Met Glu Asp Leu Val Thr Tyr  
 145 150 155 160  
 Thr Lys Asn Leu Gly Pro Gly Met Thr Lys Met Ala Lys Met Ile Asp  
 165 170 175  
 Glu Arg Gln Gln Glu Leu Thr His Gln Glu His Arg Val Met Leu Val  
 180 185 190  
 Asn Ser Met Asn Thr Val Lys Glu Leu Leu Pro Val Leu Ile Ser Ala  
 195 200 205  
 Met Lys Ile Phe Val Thr Thr Lys Asn Ser Lys Asn Gln Gly Ile Glu  
 210 215 220  
 Glu Ala Leu Lys Asn Arg Asn Phe Thr Val Glu Lys Met Ser Ala Glu  
 225 230 235 240  
 Ile Asn Glu Ile Ile Arg Val Leu Gln Leu Thr Ser Trp Asp Glu Asp  
 245 250 255  
 Ala Trp Ala Ser Lys Asp Thr Glu Ala Met Lys Arg Ala Leu Ala Ser  
 260 265 270  
 Ile Asp Ser Lys Leu Asn Gln Ala Lys Gly Trp Leu Arg Asp Pro Ser  
 275 280 285  
 Ala Ser Pro Gly Asp Ala Gly Glu Gln Ala Ile Arg Gln Ile Leu Asp  
 290 295 300  
 Glu Ala Gly Lys Val Gly Glu Leu Cys Ala Gly Lys Glu Arg Arg Glu  
 305 310 315 320  
 Ile Leu Gly Thr Cys Lys Met Leu Gly Gln Met Thr Asp Gln Val Ala  
 325 330 335  
 Asp Leu Arg Ala Arg Gly Gln Gly Ser Ser Pro Val Ala Met Gln Lys  
 340 345 350  
 Ala Gln Gln Val Ser Gln Gly Leu Asp Val Leu Thr Ala Lys Val Glu  
 355 360 365  
 Asn Ala Ala Arg Lys Leu Glu Ala Met Thr Asn Ser Lys Gln Ser Ile  
 370 375 380  
 Ala Lys Lys Ile Asp Ala Ala Gln Asn Trp Leu Ala Asp Pro Asn Gly  
 385 390 395 400

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Gly Pro Glu Gly Glu Glu Gln Ile Arg Gly Ala Leu Ala Glu Ala Arg  
 405 410 415  
 Lys Ile Ala Glu Leu Cys Asp Asp Pro Lys Glu Arg Asp Asp Ile Leu  
 420 425 430  
 Arg Ser Leu Gly Glu Ile Ser Ala Leu Thr Ser Lys Leu Ala Asp Leu  
 435 440 445  
 Arg Arg Gln Gly Lys Gly Asp Ser Pro Glu Ala Arg Ala Leu Ala Lys  
 450 455 460  
 Gln Val Ala Thr Ala Leu Gln Asn Leu Gln Thr Lys Thr Asn Arg Ala  
 465 470 475 480  
 Val Ala Asn Ser Arg Pro Ala Lys Ala Val His Leu Glu Gly Lys  
 485 490 495  
 Ile Glu Gln Ala Gln Arg Trp Ile Asp Asn Pro Thr Val Asp Asp Arg  
 500 505 510  
 Gly Val Gly Gln Ala Ala Ile Arg Gly Leu Val Ala Glu Gly His Arg  
 515 520 525  
 Leu Ala Asn Val Met Met Gly Pro Tyr Arg Gln Asp Leu Leu Ala Lys  
 530 535 540  
 Cys Asp Arg Val Asp Gln Leu Thr Ala Gln Leu Ala Asp Leu Ala Ala  
 545 550 555 560  
 Arg Gly Glu Gly Glu Ser Pro Gln Ala Arg Ala Leu Ala Ser Gln Leu  
 565 570 575  
 Gln Asp Ser Leu Lys Asp Leu Lys Ala Arg Met Gln Glu Ala Met Thr  
 580 585 590  
 Gln Glu Val Ser Asp Val Phe Ser Asp Thr Thr Thr Pro Ile Lys Leu  
 595 600 605  
 Leu Ala Val Ala Ala Thr Ala Pro Pro Asp Ala Pro Asn Arg Glu Glu  
 610 615 620  
 Val Phe Asp Glu Arg Ala Ala Asn Phe Glu Asn His Ser Gly Lys Leu  
 625 630 635 640  
 Gly Ala Thr Ala Glu Lys Ala Ala Ala Val Gly Thr Ala Asn Lys Ser  
 645 650 655  
 Thr Val Glu Gly Ile Gln Ala Ser Val Lys Thr Ala Arg Glu Leu Thr  
 660 665 670  
 Pro Gln Val Val Ser Ala Ala Arg Ile Leu Leu Arg Asn Pro Gly Asn  
 675 680 685  
 Gln Ala Ala Tyr Glu His Phe Glu Thr Met Lys Asn Gln Trp Ile Asp  
 690 695 700

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |      |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|-----|
| Asn | Val | Glu | Lys | Met | Thr | Gly | Leu | Val | Asp | Glu | Ala | Ile | Asp | Thr | Lys | 705 | 710  | 715  | 720 |
| Ser | Leu | Leu | Asp | Ala | Ser | Glu | Glu | Ala | Ile | Lys | Lys | Asp | Leu | Asp | Lys | 725 | 730  | 735  |     |
| Cys | Lys | Val | Ala | Met | Ala | Asn | Ile | Gln | Pro | Gln | Met | Leu | Val | Ala | Gly | 740 | 745  | 750  |     |
| Ala | Thr | Ser | Ile | Ala | Arg | Arg | Ala | Asn | Arg | Ile | Leu | Leu | Val | Ala | Lys | 755 | 760  | 765  |     |
| Arg | Glu | Val | Glu | Asn | Ser | Glu | Asp | Pro | Lys | Phe | Arg | Glu | Ala | Val | Lys | 770 | 775  | 780  |     |
| Ala | Ala | Ser | Asp | Glu | Leu | Ser | Lys | Thr | Ile | Ser | Pro | Met | Val | Met | Asp | 785 | 790  | 795  | 800 |
| Ala | Lys | Ala | Val | Ala | Gly | Asn | Ile | Ser | Asp | Pro | Gly | Leu | Gln | Lys | Ser | 805 | 810  |      | 815 |
| Phe | Leu | Asp | Ser | Gly | Tyr | Arg | Ile | Leu | Gly | Ala | Val | Ala | Lys | Val | Arg | 820 | 825  |      | 830 |
| Glu | Ala | Phe | Gln | Pro | Gln | Glu | Pro | Asp | Phe | Pro | Pro | Pro | Pro | Pro | Asp | 835 | 840  |      | 845 |
| Leu | Glu | Gln | Leu | Arg | Leu | Thr | Asp | Glu | Leu | Ala | Pro | Pro | Lys | Pro | Pro | 850 | 855  | 860  |     |
| Leu | Pro | Glu | Gly | Glu | Val | Pro | Pro | Pro | Arg | Pro | Pro | Pro | Pro | Glu | Glu | 865 | 870  | 875  | 880 |
| Lys | Asp | Glu | Glu | Phe | Pro | Glu | Gln | Lys | Ala | Gly | Glu | Val | Ile | Asn | Gln | 885 | 890  |      | 895 |
| Pro | Met | Met | Met | Ala | Ala | Arg | Gln | Leu | His | Asp | Glu | Ala | Arg | Lys | Trp | 900 | 905  |      | 910 |
| Ser | Ser | Lys | Gly | Asn | Asp | Ile | Ile | Ala | Ala | Ala | Lys | Arg | Met | Ala | Leu | 915 | 920  |      | 925 |
| Leu | Met | Ala | Glu | Met | Ser | Arg | Leu | Val | Arg | Gly | Gly | Ser | Gly | Thr | Lys | 930 | 935  | 940  |     |
| Arg | Ala | Leu | Ile | Gln | Cys | Ala | Lys | Asp | Ile | Ala | Lys | Ala | Ser | Asp | Glu | 945 | 950  | 955  | 960 |
| Val | Thr | Arg | Leu | Ala | Lys | Glu | Val | Ala | Lys | Gln | Cys | Thr | Asp | Lys | Arg | 965 | 970  |      | 975 |
| Ile | Arg | Thr | Asn | Leu | Leu | Gln | Val | Cys | Glu | Arg | Ile | Pro | Thr | Ile | Ser | 980 | 985  |      | 990 |
| Thr | Gln | Leu | Lys | Ile | Leu | Ser | Thr | Val | Lys | Ala | Thr | Met | Leu | Gly | Arg | 995 | 1000 | 1005 |     |



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Thr Asn Ile Ser Asp Glu Glu Ser Glu Gln Ala Thr Glu Met Leu Val  
 1010 1015 1020

His Asn Ala Gln Asn Leu Met Gln Ser Val Lys Glu Thr Val Arg Glu  
 1025 1030 1035 1040

Ala Glu Ala Ala Ser Ile Lys Ile Arg Thr Asp Ala Gly Phe Thr Leu  
 1045 1050 1055

Arg Trp Val Arg Lys Thr Pro Trp Tyr Gln  
 1060 1065

&lt;210&gt; 182

&lt;211&gt; 1666

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 182

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tggctctctt ggcagccttc ctgatttctg cagctctgtg tgaagggtgca gttttgccaa 180
ggagtgctaa agaacttaga tgtcagtgca taaagacata ctccaaacct ttccacccca 240
aatattatcaa agaactgaga gtgattgaga gtggaccaca ctgcgccaac acagaaatta 300
ttgtaaagct ttctgatgga agagagctct gtctggaccc caaggaaaac tgggtgcaga 360
gggttggtgga gaagtttttg aagagggctg agaattcata aaaaaattca ttctctgtgg 420
tatccaagaa tcagtgaaga tgccagtga aacttcaagca aatctacttc aacacttcat 480
gtattgtgtg ggtctgttgt agggttgcc gatgcaatac aagattcctg gttaaatttg 540
aatttcagta aacaatgaat agtttttcat tgtaccatga aatatccaga acatacttat 600
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gatgttatag taaattttatt ttattttaga tattaaatga tgttttatta gataaatttc 1200
aatcagggtt tttagattaa acaaacaaac aattgggtac ccagttaaatt tttcatttca 1260
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tattttaaag actgcatttt taaatacaag gctttatatt ttttaacttta agatgttttt 1560
atgtgctctc caaatttttt ttactgtttc tgattgtatg gaaatataaa agtaaatatg 1620
aaacatttaa aatataattt gttgtcaaa taaaaaaaa aaaaaa 1666

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&lt;210&gt; 183

&lt;211&gt; 99

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 183

Met Thr Ser Lys Leu Ala Val Ala Leu Leu Ala Ala Phe Leu Ile Ser  
 1 5 10 15

|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| <400> 184   |             |             |             |             |             |      |
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| ttacatagtg  | ggcgcaaaact | cccttactgc  | tttgatata   | aatccaggca  | ggaggaggta  | 120  |
| gctctaaggc  | aagagatctg  | ggacttctag  | cccctgaact  | ttcagccgaa  | tacatctttt  | 180  |
| ccaaaggagtg | gaattcaggc  | ccttgatatca | ctggcagcag  | gacgtgacca  | tggagaagct  | 240  |
| gtgtgttttc  | ttggtcttga  | ccagcctctc  | tcattgctttt | ggccagacag  | gtaagggccca | 300  |
| ccccaggcta  | tgggagagtt  | ttgatctgag  | gtatgggggt  | ggggtctaag  | actgcatgaa  | 360  |
| cagtcctcaaa | aaaaaaaaaa  | aaagactgta  | tgaacagaaac | agtggagcat  | ccttcattggt | 420  |
| gtgtgtgtgt  | gtgtgtgtgt  | gtgtgtgtgg  | tgtgtaactg  | gagaagggggt | cagtcctgttt | 480  |
| ctcaatctta  | aattctatac  | gtaagtgagg  | ggatagatct  | gtgtgatctg  | agaaacctct  | 540  |
| cacatttgct  | tgtttttctg  | gtcacagac   | atgtcgagga  | aggcttttgt  | gtttcccaaa  | 600  |
| gagtcggata  | cttcctatgt  | atccctcaaa  | gcaccgttaa  | cgaagcctct  | caaagccttc  | 660  |
| actgtgtgcc  | tccacttcta  | caaggaaactg | tcctcgaccc  | gtgggtacag  | tattttctcg  | 720  |
| tatgccacca  | agagacaaga  | caatgagatt  | ctcatatttt  | ggctctaagg  | tataggatac  | 780  |
| agttttacag  | tgggtgggtc  | tgaatatatta | ttcagggctc  | ctgaagtcac  | agtagctcca  | 840  |
| gtacacattt  | gtacaagctg  | ggagtcgcgc  | tcagggatcg  | tggagttctg  | ggtagatggg  | 900  |
| aagcccaggg  | tgaggaagag  | tctgaagaag  | ggatacactg  | tgggggcaga  | agcaagcatc  | 960  |
| atcttggggc  | aggagcagga  | ttccttcggg  | gggaactttg  | aaggaagcca  | gtccctgggtg | 1020 |
| ggagacattg  | gaaatgtgaa  | catgtgggac  | tttgtgctgt  | caccagatga  | gattaacacc  | 1080 |
| atctatcttg  | gcgggccctt  | cagtcctaata | gtcctgaact  | ggcgggcact  | gaagtatgaa  | 1140 |
| gtgcaaggcg  | aagtgttcac  | caaacccacg  | ctgtggccct  | gaggccagct  | gtgggtcctg  | 1200 |
| aaggtacctc  | ccggtttttt  | acaccgcgat  | ggccccacgt  | ctctgtctct  | ggtacctccc  | 1260 |
| gcttttttac  | actgcacgtt  | tcccacgtct  | ctgtctctg   | gcctttgttc  | ccctatatgc  | 1320 |
| attgaggcct  | gctccaccct  | cctcagcgcc  | tgagtaattga | ggtaaagtgt  | ctgtgtatgg  | 1380 |
| agctcgttaa  | ctatgctggg  | aaatgggtcca | aaagaatcag  | aatttgaggt  | gttttgtttt  | 1440 |
| cattttttatt | tcaagttgga  | cagatcttgg  | agataatttc  | ttacctcaca  | tagatgagaa  | 1500 |
| aactaacacc  | cagaaaggag  | aaatgatgtt  | ataaaaaact  | cataaggcaa  | gagctgagaa  | 1560 |
| ggaagcgctg  | atcttctatt  | taattcccca  | cccatgaccc  | ccagaaagca  | ggagcattgc  | 1620 |
| ccacattcac  | agggtctctt  | agtctcagaa  | tcaggacact  | ggccagggtg  | ctggtttggg  | 1680 |
| tccagcagta  | tcatcatcat  | gtcatagaac  | tgtctggccc  | aggtctcctg  | aaatgggaag  | 1740 |
| cccagagata  | ccacgcagtc  | cctccacttt  | ctcaaggcac  | actggaaagg  | ccattagaat  | 1800 |
| tgccccagca  | gagcagatct  | gctttttttc  | catagcaaaa  | tgaagcacta  | ggtataaata  | 1860 |
| tgttggtact  | gccaagaact  | taaatgactg  | gtttttgttt  | gctttgcagt  | ctttcttaat  | 1920 |

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tttatggctc ttctgggaaa ctccctcccct tttccacacg aacottgtgg ggctgtgaat 1980
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gatagttacg tgttcctagc aggaccaact acagtcttcc caaggattga gttatggact 2160
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ccaccagtag ccatcttggt tgccacatgg agagagactg tgaggacaga agccaaactg 2280
gaagtggagg agccaaggga ttgacaaaca acagagcctt gaccacgtgg agtctctgaa 2340
tcagccttgt ctggaaccag atctacacct ggactgcccc ggtctataag ccaataaagc 2400
ccctgtttac ttgagtgagt ccaagctggt ttctgatagt tgctttagaa gttgtgacta 2460
acttctctat gacctttgaa 2480

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&lt;210&gt; 185

&lt;211&gt; 224

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 185

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Met Glu Lys Leu Leu Cys Phe Leu Val Leu Thr Ser Leu Ser His Ala
  1             5             10             15

Phe Gly Gln Thr Asp Met Ser Arg Lys Ala Phe Val Phe Pro Lys Glu
      20             25             30

Ser Asp Thr Ser Tyr Val Ser Leu Lys Ala Pro Leu Thr Lys Pro Leu
      35             40             45

Lys Ala Phe Thr Val Cys Leu His Phe Tyr Thr Glu Leu Ser Ser Thr
      50             55             60

Arg Gly Tyr Ser Ile Phe Ser Tyr Ala Thr Lys Arg Gln Asp Asn Glu
      65             70             75             80

Ile Leu Ile Phe Trp Ser Lys Asp Ile Gly Tyr Ser Phe Thr Val Gly
      85             90             95

Gly Ser Glu Ile Leu Phe Glu Val Pro Glu Val Thr Val Ala Pro Val
      100            105            110

His Ile Cys Thr Ser Trp Glu Ser Ala Ser Gly Ile Val Glu Phe Trp
      115            120            125

Val Asp Gly Lys Pro Arg Val Arg Lys Ser Leu Lys Lys Gly Tyr Thr
      130            135            140

Val Gly Ala Glu Ala Ser Ile Ile Leu Gly Gln Glu Gln Asp Ser Phe
      145            150            155            160

Gly Gly Asn Phe Glu Gly Ser Gln Ser Leu Val Gly Asp Ile Gly Asn
      165            170            175

Val Asn Met Trp Asp Phe Val Leu Ser Pro Asp Glu Ile Asn Thr Ile
      180            185            190

Tyr Leu Gly Gly Pro Phe Ser Pro Asn Val Leu Asn Trp Arg Ala Leu
      195            200            205

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Tyr | Glu | Val | Gln | Gly | Glu | Val | Phe | Thr | Lys | Pro | Gln | Leu | Trp | Pro |
| 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |